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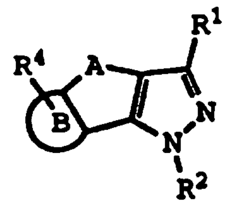
(54) Title: BENZOPYRANOPYRAZOLYL DERIVATIVES FOR THE TREATMENT OF INFLAMMATION

(57) Abstract

A class of benzopyranopyrazolyl derivatives is described for use in treating inflammation and inflammation-related disorders. Compounds of particular interest are defined by formula (I) wherein A is $-(CH_2)_m-X-(CH_2)_n-$; wherein X is $S(O)_p$ or O; wherein m is 0 or 1; wherein n is 0 or 1; wherein p is 0 or 1; wherein B is selected from phenyl and five and six membered heteroaryl; wherein R^1 is selected from lower haloalkyl, cyano, lower hydroxyalkyl, formyl, lower alkoxycarbonyl, lower alkoxy, lower N-alkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl and lower N-alkyl-N-phenylaminocarbonyl; wherein R^2 is phenyl substituted at a substitutable position with a radical selected from lower alkylsulfonyl and aminosulfonyl; and wherein R^4 is one or more radicals selected from hydrido, halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, amino, lower N-alkylamino, lower N,N-dialkylamino, lower hydroxyalkyl and lower haloalkoxy; or a pharmaceutically-acceptable salt thereof.



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BENZOPYRANOPYRAZOLYL DERIVATIVES FOR THE TREATMENT OF INFLAMMATION

FIELD OF THE INVENTION

This invention is in the field of antiinflammatory pharmaceutical agents and specifically relates to compounds, compositions and methods for treating inflammation and inflammation-associated disorders, such as arthritis.

BACKGROUND OF THE INVENTION

Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG_2, PGH_2 and PGE_2, has been a common target of antiinflammatory drug discovery. However, common non-steroidal antiinflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2 (COX-2)" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces

inflammation and produces fewer and less drastic side effects.

The novel compounds described herein are such safe and also effective antiinflammatory agents. The invention compounds are found to show usefulness *in vivo* as antiinflammatory agents with minimal side effects. The compounds described herein preferably selectively inhibit cyclooxygenase-2 over cyclooxygenase-1.

Substituted pyrazoles having antiinflammatory activity are described in copending applications 08/160,594 and 08/160,553.

U.S. Patent No. 3,940,418 to R. Hamilton describes tricyclic 4,5-dihydrobenz[g]indazole-3-carboxylic acids as antiinflammatory agents.

U.S. Patent No. 4,803,193 to Kanda et al, describes spiro[3-alkyl-1-aryl[1]benzopyrano[4,3-c]pyrazole-4(1H),9'-[9H]fluorenes as heat sensitive recording matertials.

V. Colota et al (*J.Med.Chem.*, **33**, 2646 (1991)) describe tricyclic heteroaramatic systems, including 1-aryl-pyrazolo[4,5-c]quinolin-4-ones, 1-aryl-pyrazolo[4,5-c][1,8]naphthyridin-4-ones and 1-aryl-[1]benzopyrano[3,4-d]pyrazol-4-ones for CNS aplications. F. Melani et al [*J.Med.Chem.*, **29**, 291 (1986) also describe 1-phenyl-pyrazolo[4,5-c]quinolines for CNS applications.

U.S. Patent Nos. 4,816,467 and 5,206,258 to Doria et al describe (2-cyano-3-(1,4-dihydro)-1-phenyl-[1]benzothiopyrano[4,3-c]pyrazol-3-yl)-3-oxo-propanamides as immunomodulators. G. Doria et al (*Farmaco*, **46**, 843 (1991)) also describe the immunomodulating activity of pyrazolylpropanamides, and specifically ethyl [1-(4-fluorophenyl)-1,4-dihydro-[1]benzothiopyrano[4,3-c]pyrazole]-3-carboxylate. British patent 2,227,741 describes related benzopyrano[4,3-c]pyrazoles and benzothiopyrano[4,3-

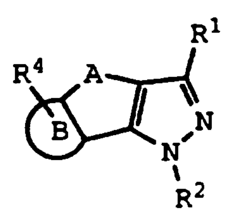
c]pyrazoles. European application No. 347,773 similarly describes such fused pyrazole compounds, and specifically α-cyano-N,1-bis(4-fluorophenyl)-β-oxo-1H-[1]benzothieno[3,2-c]pyrazole-3-propanamide. U.S. Patent No. 5,260,328 to Doria et al describes 2-cyano-3-(1,4-dihydro)-1-phenyl-[1]benzothiopyrano[4,3-c]pyrazol-3-yl)-3-oxo-propanamides for the treatment of rheumatoid arthritis.

U.S. Patent No. 4,678,499 to Pasteris et al describes 1-aryl-indenopyrazol-4-one-5-sulfonamides as having herbicidal activity. Specifically, 1-phenyl-indenopyrazol-4-one-5-sulfonamide and 1,4-dihydro-N-[[(4-methoxy-6-methyl-2-pyrimidinyl)amino]carbonyl]-3-methyl-1-[4-(methylsulfonyl)phenyl]-4-oxo-indeno[1,2-c]pyrazole-5-sulfonamide are described.

The invention's benzopyranopyrazolyl derivatives are found to show usefulness *in vivo* as antiinflammatory agents with minimal side effects.

DESCRIPTION OF THE INVENTION

A class of compounds useful in treating inflammation-related disorders is defined by Formula I:



(I)

wherein A is $-(CH_2)_m-X-(CH_2)_n-$;

wherein X is selected from $S(O)_p$, O and NR^3;

wherein m is 0 to 3, inclusive;

wherein n is 0 to 3, inclusive;

wherein p is 0 to 2, inclusive;

wherein B is selected from aryl and heteroaryl;

wherein R^1 is selected from hydrido, halo, haloalkyl, cyano, nitro, formyl, alkoxycarbonyl,

carboxyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, aminocarbonyl, alkoxy, alkoxyalkyl, aminocarbonylalkyl, N-alkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, N-alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N,N-dialkylaminosulfonyl, N-alkyl-N-arylaminosulfonyl and heterocyclic;

wherein R^2 is selected from aryl and heteroaryl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals selected from alkylsulfonyl, aminosulfonyl, halo, alkyl, alkoxy, hydroxyl and haloalkyl;

wherein R^3 is selected from hydrido and alkyl; and

wherein R^4 is one or more radicals selected from hydrido, halo, alkylthio, alkylsulfinyl, alkyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, amido, N-alkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, aminosulfonyl, N-alkylaminosulfonyl, amino, N-alkylamino, N,N-dialkylamino, heterocyclic, nitro and acylamino;

provided either R^4 is aminosulfonyl or alkylsulfonyl, or R^2 is substituted with aminosulfonyl or alkylsulfonyl;

or a pharmaceutically-acceptable salt thereof.

Compounds of Formula I would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of the invention would be useful to treat arthritis, including but not limited to rheumatoid arthritis,

spondyloarthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such compounds of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns and dermatitis. Compounds of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention of colorectal cancer. Compounds of the invention would be useful in treating inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, conjunctivitis, cystic fibrosis, swelling occurring after injury, myocardial ischemia, and the like. The compounds would also be useful in the treatment of ophthalmic diseases such as retinitis, retinopathies, uveitis, and of acute injury to the eye tissue. The compounds would also be useful for the treatment of certain central nervous system disorders such as alzheimers disease and dementia. The compounds of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These compounds would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis and central nervous system damage resulting from stroke, ischemia and trauma.

Besides being useful for human treatment, these compounds are also useful for treatment of mammals,

including horses, dogs, cats, rats, mice, sheep, and pigs, and of birds.

The present compounds may also be used in co-therapies, partially or completely, in place of other conventional antiinflammatories, such as together with steroids, NSAIDs, 5-lipoxygenase inhibitors, LTB_4 antagonists and LTA_4 hydrolase inhibitors.

Suitable LTB_4 inhibitors include, among others, ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, Terumo compound TMK-688, Lilly compounds LY-213024, 264086 and 292728, ONO compound ONO-LB457, Searle compound SC-53228, calcitrol, Lilly compounds LY-210073, LY223982, LY233469, and LY255283, ONO compound ONO-LB-448, Searle compounds SC-41930, SC-50605 and SC-51146, and SK&F compound SKF-104493. Preferably, the LTB_4 inhibitors are selected from ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, and Terumo compound TMK-688.

Suitable 5-LO inhibitors include, among others, masoprocol, tenidap, zileuton, pranlukast, tepoxalin, rilopirox, flezelastine hydrochloride, enazadrem phosphate, and bunaprolast.

The present invention preferably includes compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC_{50} of less than about 0.2 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1 μM, and more preferably of greater than 10 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

A preferred class of compounds consists of those compounds of Formula I wherein A is $-(CH_2)_m-X-(CH_2)_n-$; wherein X is selected from $S(O)_p$, O and NR^3; wherein m is 0 to 3, inclusive; wherein n is 0 to 3, inclusive; wherein p is 0 to 2, inclusive; wherein B is selected from phenyl, naphthyl and five and six membered heteroaryl; wherein R^1 is selected from halo, lower haloalkyl, cyano, nitro, formyl, lower alkoxycarbonyl, lower carboxyalkyl, lower alkoxycarbonylalkyl, amidino, cyanoamidino, lower alkoxy, lower alkoxyalkyl, aminocarbonyl, lower aminocarbonylalkyl, lower N-alkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl, lower alkylcarbonyl, lower alkylcarbonylalkyl, lower hydroxyalkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkylthioalkyl, lower alkylsulfinylalkyl, lower alkylsulfonylalkyl, lower N-alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, lower N,N-dialkylaminosulfonyl, lower N-alkyl-N-phenylaminosulfonyl and five-seven membered heterocyclic; wherein R^2 is selected from phenyl and five or six membered heteroaryl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals selected from lower alkylsulfonyl, aminosulfonyl, halo, lower alkyl, lower alkoxy, hydroxyl and lower haloalkyl; wherein R^3 is selected from hydrido and lower alkyl; and wherein R^4 is one or more radicals selected from hydrido, halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkylsulfonyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower N-alkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, aminosulfonyl, lower N-alkylaminosulfonyl, amino, lower N-alkylamino, lower N,N-dialkylamino,

five-seven membered heterocyclic, nitro and acylamino; or a pharmaceutically-acceptable salt thereof.

A more preferred class of compounds consists of those compounds of Formula I wherein A is $-(CH_2)_m-X-(CH_2)_n-$; wherein X is $S(O)_p$ or O; wherein m is 0, 1 or 2; wherein n is 0, 1 or 2; wherein p is 0, 1 or 2; wherein B is selected from phenyl and five and six membered heteroaryl; wherein R^1 is selected from halo, lower haloalkyl, cyano, formyl, lower alkoxycarbonyl, aminocarbonyl, lower alkoxycarbonylalkyl, lower alkoxy, lower alkoxyalkyl, lower aminocarbonylalkyl, lower N-alkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl and lower hydroxyalkyl; wherein R^2 is phenyl substituted at a substitutable position with a radical selected from lower alkylsulfonyl and aminosulfonyl; and wherein R^4 is one or more radicals selected from hydrido, halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkylsulfonyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower N-alkylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, amino, lower N-alkylamino, lower N,N-dialkylamino, lower haloalkoxy and nitro; or a pharmaceutically-acceptable salt thereof.

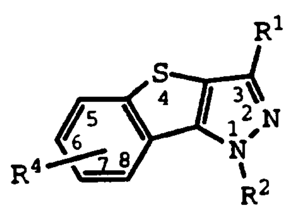
An even more preferred class of compounds consists of those compounds of Formula I wherein A is $-(CH_2)_m-X-(CH_2)_n-$; wherein X is $S(O)_p$ or O; wherein m is 0 or 1; wherein n is 0 or 1; wherein p is 0 or 1; wherein B is selected from phenyl and five and six membered heteroaryl; wherein R^1 is selected from lower haloalkyl, lower hydroxyalkyl, cyano, formyl, lower alkoxycarbonyl, lower alkoxy, lower N-alkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl and lower N-alkyl-N-phenylaminocarbonyl; wherein R^2 is phenyl substituted

at a substitutable position with a radical selected from lower alkylsulfonyl and aminosulfonyl; and wherein R^4 is one or more radicals selected from hydrido, halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, amino, lower N-alkylamino, lower N,N-dialkylamino, lower hydroxyalkyl and lower haloalkoxy; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula I wherein A is $-(CH_2)_m-X-(CH_2)_n-$; wherein X is $S(O)_p$ or O; wherein m is 0 or 1; wherein n is 0 or 1; wherein p is 0 or 1; wherein B is selected from phenyl, thienyl, pyridyl, furyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, thiaimidazolyl, oxoimidazolyl, azaoxazolyl, azathiazolyl and pyrrolyl; wherein R^1 is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxymethyl, hydroxyethyl, cyano, formyl, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, aminocarbonyl, methoxy, ethoxy, propoxy, n-butoxy, N-methylaminocarbonyl, N-phenylaminocarbonyl, N,N-dimethylaminocarbonyl, N-methyl-N-phenylaminocarbonyl and methylcarbonyl; wherein R^2 is phenyl substituted at a substitutable position with a radical selected from methylsulfonyl and aminosulfonyl; wherein R^4 is optionally substituted with one or more radicals selected from hydrido, fluoro, chloro, bromo, methylthio, ethylthio, isopropylthio, *tert*-butylthio,

isobutylthio, hexylthio, methylsulfinyl, ethylsulfinyl, isopropylsulfinyl, *tert*-butylsulfinyl, isobutylsulfinyl, hexylsulfinyl, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, hexyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, aminocarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, hydroxymethyl and trifluoromethoxy; or a pharmaceutically-acceptable salt thereof.

The preferred compounds of Formula I can be represented by Formulas Ia-Ip as follows:



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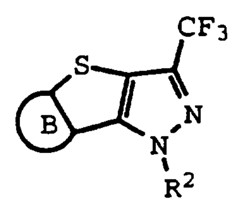

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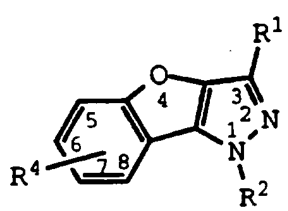

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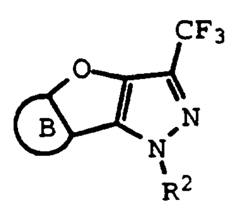

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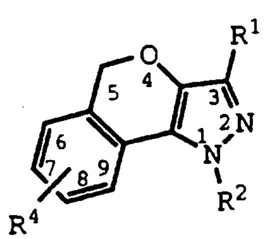

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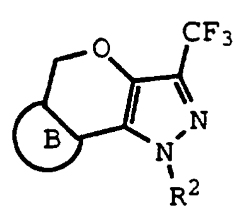

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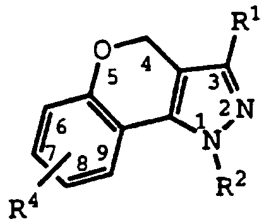

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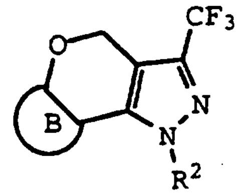

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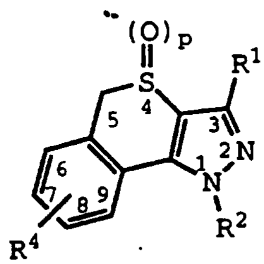

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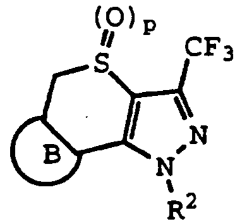

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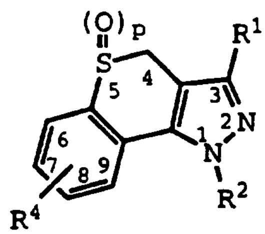

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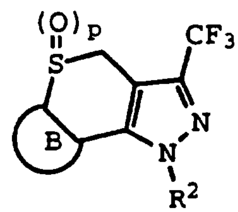

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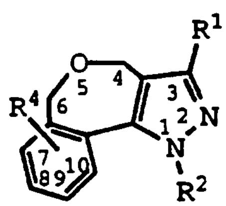

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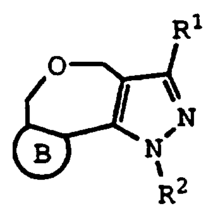

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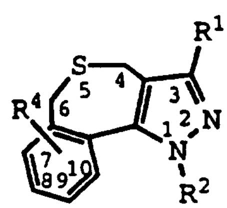
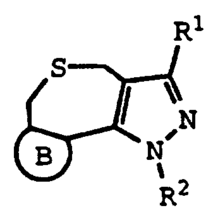


(Io)

and



(Ip)

A family of specific compounds of particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts thereof as shown in the following Tables:

TABLE I

General Structure Ia

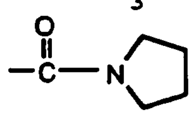
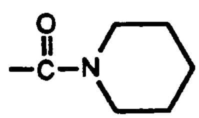
R^1	R^2	R^4
$-CF_3$	$C_6H_5SO2CH3$	H
$-CF_2H$	$C_6H_5SO2CH3$	H
$-CF_2Cl$	$C_6H_5SO2CH3$	H
$-CF_2CF_3$	$C_6H_5SO2CH3$	H
$-CO_2H$	$C_6H_5SO2CH3$	H
$-CO_2CH_3$	$C_6H_5SO2CH3$	H
$-CO_2C_2H_5$	$C_6H_5SO2CH3$	H
$-CONH_2$	$C_6H_5SO2CH3$	H
$-CONHCH_3$	$C_6H_5SO2CH3$	H
$-CONH(C_6H_3)$	$C_6H_5SO2CH3$	H
$-CON(CH_3)_2$	$C_6H_5SO2CH3$	H
$-CON(C_2H_5)_2$	$C_6H_5SO2CH3$	H
$-CON(CH_3)(C_2H_5)$	$C_6H_5SO2CH3$	H
$-CON(CH_3)(C_6H_5)$	$C_6H_5SO2CH3$	H
	$C_6H_5SO2CH3$	H
	$C_6H_5SO2CH3$	H
$-CN$	$C_6H_5SO2CH3$	H
$-CH_2OH$	$C_6H_5SO2CH3$	H
$-CH_2OCH_3$	$C_6H_5SO2CH3$	H
$-CH_2OC_2H_5$	$C_6H_5SO2CH3$	H
$-CH_2OC_6H_5$	$C_6H_5SO2CH3$	H
$-CH_2SCH_3$	$C_6H_5SO2CH3$	H
$-CH_2SC_2H_5$	$C_6H_5SO2CH3$	H
$-CH_2SC_6H_5$	$C_6H_5SO2CH3$	H
$-CH_2SOCH_3$	$C_6H_5SO2CH3$	H
$-CH_2SOC_2H_5$	$C_6H_5SO2CH3$	H
$-CH_2SOC_6H_5$	$C_6H_5SO2CH3$	H
$-CH_2SO_2CH_3$	$C_6H_5SO2CH3$	H

TABLE I (cont.)

General Structure Ia

R^1	R^2	R^4
$-CH_2SO_2C_2H_5$	$C_6H_5SO2CH3$	H
$-CH_2SO_2C_6H_5$	$C_6H_5SO2CH3$	H
$-CF_3$	$C_6H_5SO2CH3$	5-F
$-CF_3$	$C_6H_5SO2CH3$	7-F
$-CF_3$	$C_6H_5SO2CH3$	6-F
$-CF_3$	$C_6H_5SO2CH3$	7-Cl
$-CF_3$	$C_6H_5SO2CH3$	6-Cl
$-CF_3$	$C_6H_5SO2CH3$	6,7-(OCH2O)-
$-CF_3$	$C_6H_5SO2CH3$	6-N(CH3)2
$-CF_3$	$C_6H_5SO2CH3$	6-OCH3
$-CF_3$	$C_6H_5SO2CH3$	5-F, 6-OCH3
$-CF_3$	$C_6H_5SO2CH3$	5-Cl, 6-OCH3
$-CF_3$	$C_6H_5SO2CH3$	6-Cl, 5-F
$-CF_3$	$C_6H_5SO2CH3$	6-CH3
$-CF_3$	$C_6H_5SO2CH3$	5-F, 6-CH3
$-CF_3$	$C_6H_5SO2CH3$	5,6-F
$-CF_3$	$C_6H_5SO2CH3$	6-SCH3
$-CF_3$	$C_6H_5SO2CH3$	5-F, 6-SCH3
$-CF_3$	$C_6H_5SO2CH3$	6-SOCH3
$-CF_3$	$C_6H_5SO2CH3$	5-F, 6-SOCH3
$-CF_3$	$C_6H_5SO2CH3$	5-F, 6-CH3
$-CF_3$	C_6H_5F	6-SO2CH3
$-CF_3$	C_6H_5Cl	6-SO2CH3
$-CF_3$	C_6H_5OCH3	6-SO2CH3
$-CF_3$	C_6H_5CH3	6-SO2CH3
$-CF_3$	C_6H_5SOCH3	6-SO2CH3
$-CF_3$	$C_6H_5SO2NH2$	H
$-CF_2H$	$C_6H_5SO2NH2$	H
$-CF_2Cl$	$C_6H_5SO2NH2$	H
$-CF_2CF_3$	$C_6H_5SO2NH2$	H
$-CO_2H$	$C_6H_5SO2NH2$	H
$-CO_2CH_3$	$C_6H_5SO2NH2$	H

TABLE I (cont.)

General Structure Ia

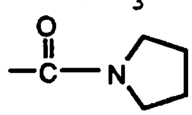
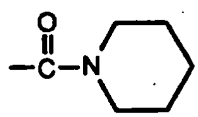
R^1	R^2	R^4
$-CO_2C_2H_5$	$C_6H_5SO2NH2$	H
$-CONH_2$	$C_6H_5SO2NH2$	H
$-CONHCH_3$	$C_6H_5SO2NH2$	H
$-CONH(C_6H_3)$	$C_6H_5SO2NH2$	H
$-CON(CH_3)_2$	$C_6H_5SO2NH2$	H
$-CON(C_2H_5)_2$	$C_6H_5SO2NH2$	H
$-CON(CH_3)(C_2H_5)$	$C_6H_5SO2NH2$	H
$-CON(CH_3)(C_6H_5)$	$C_6H_5SO2NH2$	H
	$C_6H_5SO2NH2$	H
	$C_6H_5SO2NH2$	H
-CN	$C_6H_5SO2NH2$	H
$-CH_2OH$	$C_6H_5SO2NH2$	H
$-CH_2OCH_3$	$C_6H_5SO2NH2$	H
$-CH_2OC_2H_5$	$C_6H_5SO2NH2$	H
$-CH_2OC_6H_5$	$C_6H_5SO2NH2$	H
$-CH_2SCH_3$	$C_6H_5SO2NH2$	H
$-CH_2SC_2H_5$	$C_6H_5SO2NH2$	H
$-CH_2SC_6H_5$	$C_6H_5SO2NH2$	H
$-CH_2SOCH_3$	$C_6H_5SO2NH2$	H
$-CH_2SOC_6H_5$	$C_6H_5SO2NH2$	H
$-CH_2SO_2CH_3$	$C_6H_5SO2NH2$	H
$-CH_2SO_2C_2H_5$	$C_6H_5SO2NH2$	H
$-CH_2SO_2C_6H_5$	$C_6H_5SO2NH2$	H
$-CF_3$	$C_6H_5SO2NH2$	5-F
$-CF_3$	$C_6H_5SO2NH2$	7-F
$-CF_3$	$C_6H_5SO2NH2$	6-F
$-CF_3$	$C_6H_5SO2NH2$	7-Cl
$-CF_3$	$C_6H_5SO2NH2$	6-Cl

TABLE I (cont.)

General Structure Ia

R^1	R^2	R^4
$-CF_3$	$C_6H_5SO_2NH_2$	6,7-(OCH_2O)-
$-CF_3$	$C_6H_5SO_2NH_2$	6-$N(CH_3)_2$
$-CF_3$	$C_6H_5SO_2NH_2$	6-OCH_3
$-CF_3$	$C_6H_5SO_2NH_2$	5-F, 6-OCH_3
$-CF_3$	$C_6H_5SO_2NH_2$	5-Cl, 6-OCH_3
$-CF_3$	$C_6H_5SO_2NH_2$	6-Cl, 5-F
$-CF_3$	$C_6H_5SO_2NH_2$	6-CH_3
$-CF_3$	$C_6H_5SO_2NH_2$	5-F, 6-CH_3
$-CF_3$	$C_6H_5SO_2NH_2$	5,6-F
$-CF_3$	$C_6H_5SO_2NH_2$	6-SCH_3
$-CF_3$	$C_6H_5SO_2NH_2$	5-F, 6-SCH_3
$-CF_3$	$C_6H_5SO_2NH_2$	6-$SOCH_3$
$-CF_3$	$C_6H_5SO_2NH_2$	5-F, 6-$SOCH_3$
$-CF_3$	$C_6H_5SO_2NH_2$	5-F, 6-CH_3
$-CF_3$	C_6H_5F	6-SO_2NH_2
$-CF_3$	C_6H_5Cl	6-SO_2NH_2
$-CF_3$	$C_6H_5OCH_3$	6-SO_2NH_2
$-CF_3$	$C_6H_5CH_3$	6-SO_2NH_2
$-CF_3$	$C_6H_5SOCH_3$	6-SO_2NH_2
$-CF_3$	thienylSO_2NH_2	5-F, 6-OCH_3

TABLE II

General Structure Ib

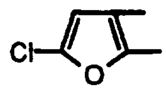
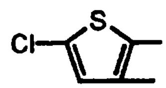
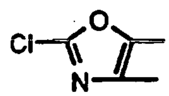
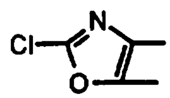
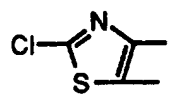
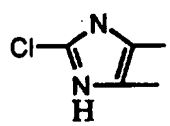
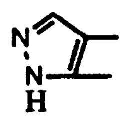
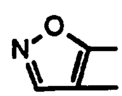
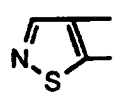
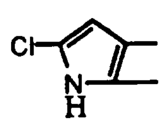
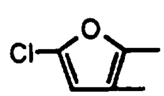
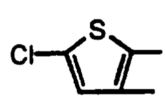
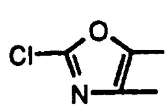
B	R^2
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$

TABLE II (cont.)

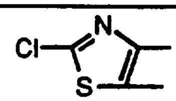
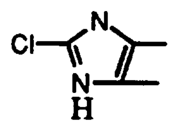
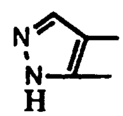
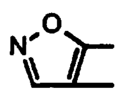
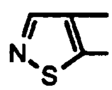
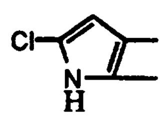
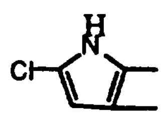
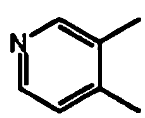
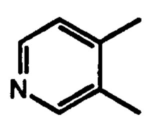
B	R^2
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$

TABLE III
General Structure Ic

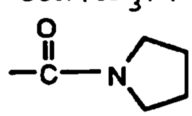
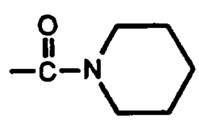
R^1	R^2	R^4
$-CF_3$	C_6H_5SO2CH3	H
$-CF_2H$	C_6H_5SO2CH3	H
$-CF_2Cl$	C_6H_5SO2CH3	H
$-CF_2CF_3$	C_6H_5SO2CH3	H
$-CO_2H$	C_6H_5SO2CH3	H
$-CO_2CH_3$	C_6H_5SO2CH3	H
$-CO_2C_2H_5$	C_6H_5SO2CH3	H
$-CONH_2$	C_6H_5SO2CH3	H
$-CONHCH_3$	C_6H_5SO2CH3	H
$-CONH(C_6H_3)$	C_6H_5SO2CH3	H
$-CON(CH_3)_2$	C_6H_5SO2CH3	H
$-CON(C_2H_5)_2$	C_6H_5SO2CH3	H
$-CON(CH_3)(C_2H_5)$	C_6H_5SO2CH3	H
$-CON(CH_3)(C_6H_5)$	C_6H_5SO2CH3	H
	C_6H_5SO2CH3	H
	C_6H_5SO2CH3	H
-CN	C_6H_5SO2CH3	H
$-CH_2OH$	C_6H_5SO2CH3	H
$-CH_2OCH_3$	C_6H_5SO2CH3	H
$-CH_2OC_2H_5$	C_6H_5SO2CH3	H
$-CH_2OC_6H_5$	C_6H_5SO2CH3	H
$-CH_2SCH_3$	C_6H_5SO2CH3	H
$-CH_2SC_2H_5$	C_6H_5SO2CH3	H
$-CH_2SC_6H_5$	C_6H_5SO2CH3	H
$-CH_2SOCH_3$	C_6H_5SO2CH3	H
$-CH_2SOC_2H_5$	C_6H_5SO2CH3	H
$-CH_2SOC_6H_5$	C_6H_5SO2CH3	H
$-CH_2SO_2CH_3$	C_6H_5SO2CH3	H
$-CH_2SO_2C_2H_5$	C_6H_5SO2CH3	H

TABLE III (cont.)
General Structure Ic

R^1	R^2	R^4
$-CH_2SO_2C_6H_5$	$C_6H_5SO2CH3$	H
$-CF_3$	$C_6H_5SO2CH3$	5-F
$-CF_3$	$C_6H_5SO2CH3$	7-F
$-CF_3$	$C_6H_5SO2CH3$	6-F
$-CF_3$	$C_6H_5SO2CH3$	7-Cl
$-CF_3$	$C_6H_5SO2CH3$	6-Cl
$-CF_3$	$C_6H_5SO2CH3$	6,7-(OCH2O)-
$-CF_3$	$C_6H_5SO2CH3$	6-N(CH3)2
$-CF_3$	$C_6H_5SO2CH3$	6-OCH3
$-CF_3$	$C_6H_5SO2CH3$	5-F, 6-OCH3
$-CF_3$	$C_6H_5SO2CH3$	5-Cl, 6-OCH3
$-CF_3$	$C_6H_5SO2CH3$	6-Cl, 5-F
$-CF_3$	$C_6H_5SO2CH3$	6-CH3
$-CF_3$	$C_6H_5SO2CH3$	5-F, 6-CH3
$-CF_3$	$C_6H_5SO2CH3$	5,6-F
$-CF_3$	$C_6H_5SO2CH3$	6-SCH3
$-CF_3$	$C_6H_5SO2CH3$	5-F, 6-SCH3
$-CF_3$	$C_6H_5SO2CH3$	6-SOCH3
$-CF_3$	$C_6H_5SO2CH3$	5-F, 6-SOCH3
$-CF_3$	$C_6H_5SO2CH3$	5-F, 6-CH3
$-CF_3$	C_6H_5F	6-SO2CH3
$-CF_3$	C_6H_5Cl	6-SO2CH3
$-CF_3$	C_6H_5OCH3	6-SO2CH3
$-CF_3$	C_6H_5CH3	6-SO2CH3
$-CF_3$	C_6H_5SOCH3	6-SO2CH3
$-CF_3$	$C_6H_5SO2NH2$	H
$-CF_2H$	$C_6H_5SO2NH2$	H
$-CF_2Cl$	$C_6H_5SO2NH2$	H
$-CF_2CF_3$	$C_6H_5SO2NH2$	H
$-CO_2H$	$C_6H_5SO2NH2$	H
$-CO_2CH_3$	$C_6H_5SO2NH2$	H
$-CO_2C_2H_5$	$C_6H_5SO2NH2$	H

TABLE III (c nt.)
General Structure Ic

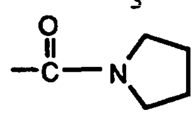
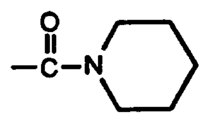
R^1	R^2	R^4
$-CONH_2$	C_6H_5SO2NH2	H
$-CONHCH_3$	C_6H_5SO2NH2	H
$-CONH(C_6H_3)$	C_6H_5SO2NH2	H
$-CON(CH_3)_2$	C_6H_5SO2NH2	H
$-CON(C_2H_5)_2$	C_6H_5SO2NH2	H
$-CON(CH_3)(C_2H_5)$	C_6H_5SO2NH2	H
$-CON(CH_3)(C_6H_5)$	C_6H_5SO2NH2	H
	C_6H_5SO2NH2	H
	C_6H_5SO2NH2	H
-CN	C_6H_5SO2NH2	H
$-CH_2OH$	C_6H_5SO2NH2	H
$-CH_2OCH_3$	C_6H_5SO2NH2	H
$-CH_2OC_2H_5$	C_6H_5SO2NH2	H
$-CH_2OC_6H_5$	C_6H_5SO2NH2	H
$-CH_2SCH_3$	C_6H_5SO2NH2	H
$-CH_2SC_2H_5$	C_6H_5SO2NH2	H
$-CH_2SC_6H_5$	C_6H_5SO2NH2	H
-CH2SOC6H5	C_6H_5SO2NH2	H
$-CH_2SO_2CH_3$	C_6H_5SO2NH2	H
$-CH_2SO_2C_2H_5$	C_6H_5SO2NH2	H
$-CH_2SO_2C_6H_5$	C_6H_5SO2NH2	H
$-CF_3$	C_6H_5SO2NH2	5-F
$-CF_3$	C_6H_5SO2NH2	7-F
$-CF_3$	C_6H_5SO2NH2	6-F
$-CF_3$	C_6H_5SO2NH2	7-Cl
$-CF_3$	C_6H_5SO2NH2	6-Cl
$-CF_3$	C_6H_5SO2NH2	6,7-(OCH2O)-
$-CF_3$	C_6H_5SO2NH2	6-N(CH3)2
$-CF_3$	C_6H_5SO2NH2	6-OCH3

TABLE III (cont.)
General Structure Ic

R^1	R^2	R^4
$-CF_3$	$C_6H_5SO_2NH_2$	5-F, 6-OCH_3
$-CF_3$	$C_6H_5SO_2NH_2$	5-Cl, 6-OCH_3
$-CF_3$	$C_6H_5SO_2NH_2$	6-Cl, 5-F
$-CF_3$	$C_6H_5SO_2NH_2$	6-CH_3
$-CF_3$	$C_6H_5SO_2NH_2$	5-F, 6-CH_3
$-CF_3$	$C_6H_5SO_2NH_2$	5,6-F
$-CF_3$	$C_6H_5SO_2NH_2$	6-SCH_3
$-CF_3$	$C_6H_5SO_2NH_2$	5-F, 6-SCH_3
$-CF_3$	$C_6H_5SO_2NH_2$	6-$SOCH_3$
$-CF_3$	$C_6H_5SO_2NH_2$	5-F, 6-$SOCH_3$
$-CF_3$	$C_6H_5SO_2NH_2$	5-F, 6-CH_3
$-CF_3$	C_6H_5F	6-SO_2NH_2
$-CF_3$	C_6H_5Cl	6-SO_2NH_2
$-CF_3$	$C_6H_5OCH_3$	6-SO_2NH_2
$-CF_3$	$C_6H_5CH_3$	6-SO_2NH_2
$-CF_3$	$C_6H_5SOCH_3$	6-SO_2NH_2
$-CF_3$	thienylSO_2NH_2	5-F, 6-OCH_3

TABLE IV

General Structure Id

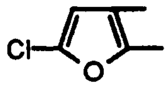
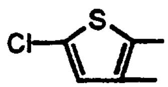
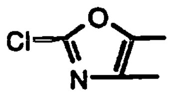
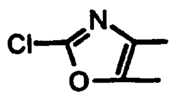
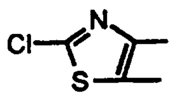
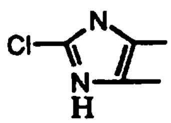
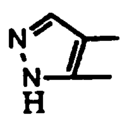
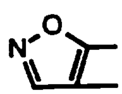
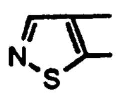
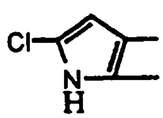
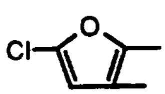
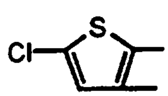
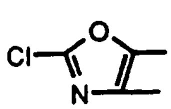
B	R^2
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$

TABLE IV (cont.)

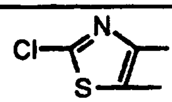
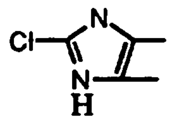
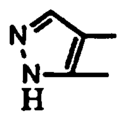
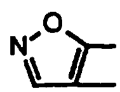
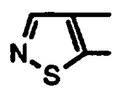
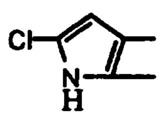
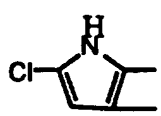
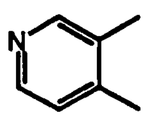
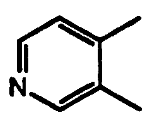
B	R^2
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$

TABLE V

General Structure Ie

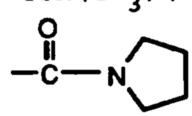
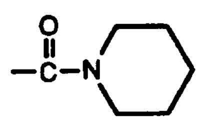
R^1	R^2	R^4
$-CF_3$	$-C_6H_5SO_2CH_3$	H
$-CF_2H$	$-C_6H_5SO_2CH_3$	H
$-CF_2Cl$	$-C_6H_5SO_2CH_3$	H
$-CF_2CF_3$	$-C_6H_5SO_2CH_3$	H
$-CO_2H$	$-C_6H_5SO_2CH_3$	H
$-CO_2CH_3$	$-C_6H_5SO_2CH_3$	H
$-CO_2C_2H_5$	$-C_6H_5SO_2CH_3$	H
$-CONH_2$	$-C_6H_5SO_2CH_3$	H
$-CONHCH_3$	$-C_6H_5SO_2CH_3$	H
$-CONH(C_6H_3)$	$-C_6H_5SO_2CH_3$	H
$-CON(CH_3)_2$	$-C_6H_5SO_2CH_3$	H
$-CON(C_2H_5)_2$	$-C_6H_5SO_2CH_3$	H
$-CON(CH_3)(C_2H_5)$	$-C_6H_5SO_2CH_3$	H
$-CON(CH_3)(C_6H_5)$	$-C_6H_5SO_2CH_3$	H
	$-C_6H_5SO_2CH_3$	H
	$-C_6H_5SO_2CH_3$	H
$-CN$	$-C_6H_5SO_2CH_3$	H
$-CH_2OH$	$-C_6H_5SO_2CH_3$	H
$-CH_2OCH_3$	$-C_6H_5SO_2CH_3$	H
$-CH_2OC_2H_5$	$-C_6H_5SO_2CH_3$	H
$-CH_2OC_6H_5$	$-C_6H_5SO_2CH_3$	H
$-CH_2SCH_3$	$-C_6H_5SO_2CH_3$	H
$-CH_2SC_2H_5$	$-C_6H_5SO_2CH_3$	H
$-CH_2SC_6H_5$	$-C_6H_5SO_2CH_3$	H
$-CH_2SOCH_3$	$-C_6H_5SO_2CH_3$	H
$-CH_2SOC_2H_5$	$-C_6H_5SO_2CH_3$	H

TABLE V (cont.)

General Structure Ie

R^1	R^2	R^4
$-CH_2SOC_6H_5$	$-C_6H_5SO_2CH_3$	H
$-CH_2SO_2CH_3$	$-C_6H_5SO_2CH_3$	H
$-CH_2SO_2C_2H_5$	$-C_6H_5SO_2CH_3$	H
$-CH_2SO_2C_6H_5$	$-C_6H_5SO_2CH_3$	H
$-CF_3$	$-C_6H_5SO_2CH_3$	6-F
$-CF_3$	$-C_6H_5SO_2CH_3$	7-F
$-CF_3$	$-C_6H_5SO_2CH_3$	8-F
$-CF_3$	$-C_6H_5SO_2CH_3$	7-Cl
$-CF_3$	$-C_6H_5SO_2CH_3$	8-Cl
$-CF_3$	$-C_6H_5SO_2CH_3$	7,8-(OCH_2O)-
$-CF_3$	$-C_6H_5SO_2CH_3$	7-$N(CH_3)_2$
$-CF_3$	$-C_6H_5SO_2CH_3$	7-OCH_3
$-CF_3$	$-C_6H_5SO_2CH_3$	6-F, 7-OCH_3
$-CF_3$	$-C_6H_5SO_2CH_3$	6-Cl, 7-OCH_3
$-CF_3$	$-C_6H_5SO_2CH_3$	7-Cl, 6-F
$-CF_3$	$-C_6H_5SO_2CH_3$	7-CH_3
$-CF_3$	$-C_6H_5SO_2CH_3$	6-F, 7-CH_3
$-CF_3$	$-C_6H_5SO_2CH_3$	6,7-F
$-CF_3$	$-C_6H_5SO_2CH_3$	7-SCH_3
$-CF_3$	$-C_6H_5SO_2CH_3$	6-F, 7-SCH_3
$-CF_3$	$-C_6H_5SO_2CH_3$	7-$SOCH_3$
$-CF_3$	$-C_6H_5SO_2CH_3$	6-F, 7-$SOCH_3$
$-CF_3$	$-C_6H_5SO_2CH_3$	6-F, 7-CH_3
$-CF_3$	$-C_6H_5F$	7-SO_2CH_3
$-CF_3$	$-C_6H_5Cl$	7-SO_2CH_3
$-CF_3$	$-C_6H_5OCH_3$	7-SO_2CH_3
$-CF_3$	$-C_6H_5CH_3$	7-SO_2CH_3
$-CF_3$	$-C_6H_5SOCH_3$	7-SO_2CH_3

TABLE V (cont.)

General Structure Ie

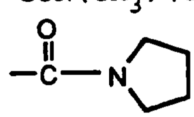
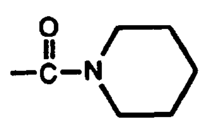
R^1	R^2	R^4
$-CF_3$	$-C_6H_5SO2NH2$	H
$-CF_2H$	$-C_6H_5SO2NH2$	H
$-CF_2Cl$	$-C_6H_5SO2NH2$	H
$-CF_2CF_3$	$-C_6H_5SO2NH2$	H
$-CO_2H$	$-C_6H_5SO2NH2$	H
$-CO_2CH_3$	$-C_6H_5SO2NH2$	H
$-CO_2C_2H_5$	$-C_6H_5SO2NH2$	H
$-CONH_2$	$-C_6H_5SO2NH2$	H
$-CONHCH_3$	$-C_6H_5SO2NH2$	H
$-CONH(C_6H_3)$	$-C_6H_5SO2NH2$	H
$-CON(CH_3)_2$	$-C_6H_5SO2NH2$	H
$-CON(C_2H_5)_2$	$-C_6H_5SO2NH2$	H
$-CON(CH_3)(C_2H_5)$	$-C_6H_5SO2NH2$	H
$-CON(CH_3)(C_6H_5)$	$-C_6H_5SO2NH2$	H
	$-C_6H_5SO2NH2$	H
	$-C_6H_5SO2NH2$	H
$-CN$	$-C_6H_5SO2NH2$	H
$-CH_2OH$	$-C_6H_5SO2NH2$	H
$-CH_2OCH_3$	$-C_6H_5SO2NH2$	H
$-CH_2OC_2H_5$	$-C_6H_5SO2NH2$	H
$-CH_2OC_6H_5$	$-C_6H_5SO2NH2$	H
$-CH_2SCH_3$	$-C_6H_5SO2NH2$	H
$-CH_2SC_2H_5$	$-C_6H_5SO2NH2$	H
$-CH_2SC_6H_5$	$-C_6H_5SO2NH2$	H
$-CH_2SOCH_3$	$-C_6H_5SO2NH2$	H
$-CH_2SOC_2H_5$	$-C_6H_5SO2NH2$	H

TABLE V (cont.)

General Structure Ie

R^1	R^2	R^4
$-CH_2SOC_6H_5$	$-C_6H_5SO2NH2$	H
$-CH_2SO_2CH_3$	$-C_6H_5SO2NH2$	H
$-CH_2SO_2C_2H_5$	$-C_6H_5SO2NH2$	H
$-CH_2SO_2C_6H_5$	$-C_6H_5SO2NH2$	H
$-CF_3$	$-C_6H_5SO2NH2$	6-F
$-CF_3$	$-C_6H_5SO2NH2$	7-F
$-CF_3$	$-C_6H_5SO2NH2$	8-F
$-CF_3$	$-C_6H_5SO2NH2$	7-Cl
$-CF_3$	$-C_6H_5SO2NH2$	8-Cl
$-CF_3$	$-C_6H_5SO2NH2$	7,8-(OCH2O)-
$-CF_3$	$-C_6H_5SO2NH2$	7-N(CH3)2
$-CF_3$	$-C_6H_5SO2NH2$	7-OCH3
$-CF_3$	$-C_6H_5SO2NH2$	6-F, 7-OCH3
$-CF_3$	$-C_6H_5SO2NH2$	6-Cl, 7-OCH3
$-CF_3$	$-C_6H_5SO2NH2$	7-Cl, 6-F
$-CF_3$	$-C_6H_5SO2NH2$	7-CH3
$-CF_3$	$-C_6H_5SO2NH2$	6-F, 7-CH3
$-CF_3$	$-C_6H_5SO2NH2$	6,7-F
$-CF_3$	$-C_6H_5SO2NH2$	7-SCH3
$-CF_3$	$-C_6H_5SO2NH2$	6-F, 7-SCH3
$-CF_3$	$-C_6H_5SO2NH2$	7-SOCH3
$-CF_3$	$-C_6H_5SO2NH2$	6-F, 7-SOCH3
$-CF_3$	$-C_6H_5SO2NH2$	6-F, 7-CH3
$-CF_3$	$--C_6H_5SO_2NH_2$	6-F, 7-OCH_3
$-CF_3$	$-C_6H_5SO2NH2$	7,8,9-OCH3
$-CF_3$	$-C_6H_5F$	7-SO2NH2
$-CF_3$	$-C_6H_5Cl$	7-SO2NH2
$-CF_3$	$-C_6H_5OCH3$	7-SO2NH2
$-CF_3$	$-C_6H_5CH3$	7-SO2NH2
$-CF_3$	$-C_6H_5SOCH3$	7-SO2NH2
$-CF_2H$	$-C_6H_5SO2NH2$	7-CH3

TABLE VI

General Structure If

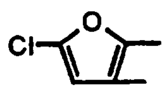
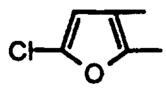
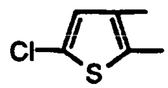
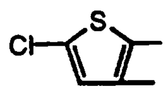
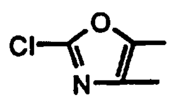
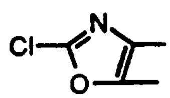
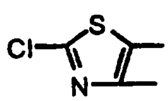
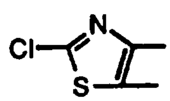
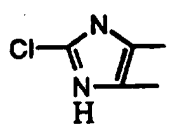
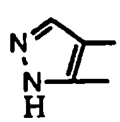
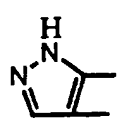
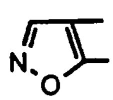
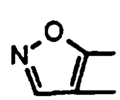
B	R^2
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$

TABLE VI (cont.)

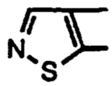
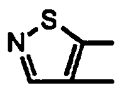
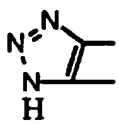
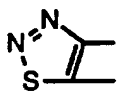
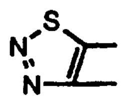
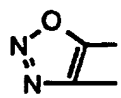
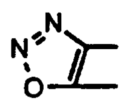
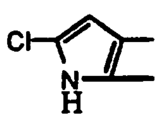
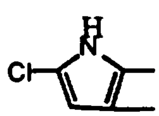
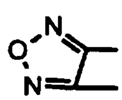
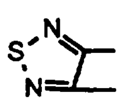
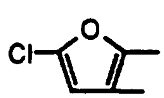
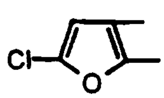
B	R^2
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$

TABLE VI (cont.)

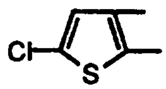
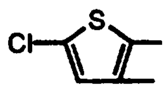
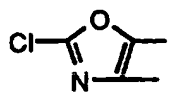
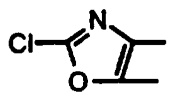
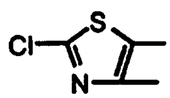
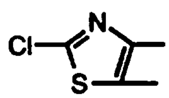
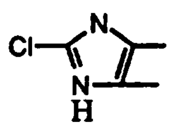
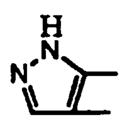
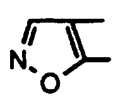
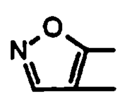
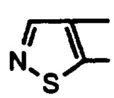
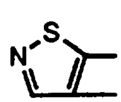
B	R^2
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$

TABLE VI (cont.)

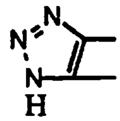
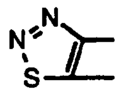
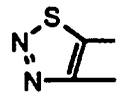
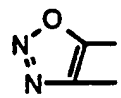
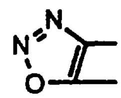
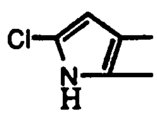
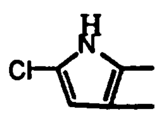
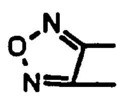
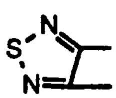
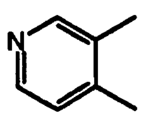
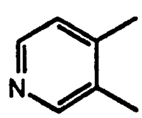
B	R^2
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$

TABLE VII

General Structure Ig

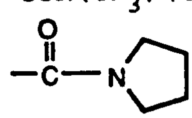
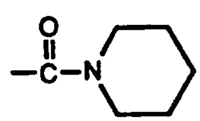
R^1	R^2	R^4
$-CF_3$	$-C_6H_5SO2CH_3$	H
$-CF_2H$	$-C_6H_5SO2CH_3$	H
$-CF_2Cl$	$-C_6H_5SO2CH_3$	H
$-CF_2CF_3$	$-C_6H_5SO2CH_3$	H
$-CO_2H$	$-C_6H_5SO2CH_3$	H
$-CO_2CH_3$	$-C_6H_5SO2CH_3$	H
$-CO_2C_2H_5$	$-C_6H_5SO2CH_3$	H
$-CONH_2$	$-C_6H_5SO2CH_3$	H
$-CONHCH_3$	$-C_6H_5SO2CH_3$	H
$-CONH(C_6H_3)$	$-C_6H_5SO2CH_3$	H
$-CON(CH_3)_2$	$-C_6H_5SO2CH_3$	H
$-CON(C_2H_5)_2$	$-C_6H_5SO2CH_3$	H
$-CON(CH_3)(C_2H_5)$	$-C_6H_5SO2CH_3$	H
$-CON(CH_3)(C_6H_5)$	$-C_6H_5SO2CH_3$	H
	$-C_6H_5SO2CH_3$	H
	$-C_6H_5SO2CH_3$	H
$-CN$	$-C_6H_5SO2CH_3$	H
$-CH_2OH$	$-C_6H_5SO2CH_3$	H
$-CH_2OCH_3$	$-C_6H_5SO2CH_3$	H
$-CH_2OC_2H_5$	$-C_6H_5SO2CH_3$	H
$-CH_2OC_6H_5$	$-C_6H_5SO2CH_3$	H
$-CH_2SCH_3$	$-C_6H_5SO2CH_3$	H
$-CH_2SC_2H_5$	$-C_6H_5SO2CH_3$	H
$-CH_2SC_6H_5$	$-C_6H_5SO2CH_3$	H
$-CH_2SOCH_3$	$-C_6H_5SO2CH_3$	H
$-CH_2SOC_2H_5$	$-C_6H_5SO2CH_3$	H
$-CH_2SOC_6H_5$	$-C_6H_5SO2CH_3$	H
$-CH_2SO_2CH_3$	$-C_6H_5SO2CH_3$	H

TABLE VII (cont.)

General Structure Ig

R^1	R^2	R^4
$-CH_2SO_2C_2H_5$	$-C_6H_5SO2CH_3$	H
$-CH_2SO_2C_6H_5$	$-C_6H_5SO2CH_3$	H
$-CF_3$	$-C_6H_5SO2CH_3$	6-F
$-CF_3$	$-C_6H_5SO2CH_3$	7-F
$-CF_3$	$-C_6H_5SO2CH_3$	8-F
$-CF_3$	$-C_6H_5SO2CH_3$	7-Cl
$-CF_3$	$-C_6H_5SO2CH_3$	8-Cl
$-CF_3$	$-C_6H_5SO2CH_3$	7,8-(OCH2O)-
$-CF_3$	$-C_6H_5SO2CH_3$	7-N(CH3)2
$-CF_3$	$-C_6H_5SO2CH_3$	7-OCH3
$-CF_3$	$-C_6H_5SO2CH_3$	6-F, 7-OCH3
$-CF_3$	$-C_6H_5SO2CH_3$	6-Cl, 7-OCH3
$-CF_3$	$-C_6H_5SO2CH_3$	7-Cl, 6-F
$-CF_3$	$-C_6H_5SO2CH_3$	7-CH3
$-CF_3$	$-C_6H_5SO2CH_3$	6-F, 7-CH3
$-CF_3$	$-C_6H_5SO2CH_3$	6,7-F
$-CF_3$	$-C_6H_5SO2CH_3$	7-SCH3
$-CF_3$	$-C_6H_5SO2CH_3$	6-F, 7-SCH3
$-CF_3$	$-C_6H_5SO2CH_3$	7-SOCH3
$-CF_3$	$-C_6H_5SO2CH_3$	6-F, 7-SOCH3
$-CF_3$	$-C_6H_5SO2CH_3$	6-F, 7-CH3
$-CF_3$	$-C_6H_5F$	7-SO2CH3
$-CF_3$	$-C_6H_5Cl$	7-SO2CH3
$-CF_3$	$-C_6H_5OCH3$	7-SO2CH3
$-CF_3$	$-C_6H_5CH3$	7-SO2CH3
$-CF_3$	$-C_6H_5SONH3$	7-SO2CH3
$-CF_3$	$-C_6H_5SO2NH_3$	H
$-CF_2H$	$-C_6H_5SO2NH_3$	H
$-CF_2Cl$	$-C_6H_5SO2NH_3$	H
$-CF_2CF_3$	$-C_6H_5SO2NH_3$	H

TABLE VII (cont.)

General Structure Ig

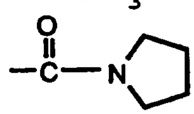
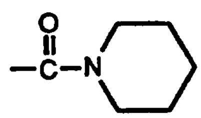
R^1	R^2	R^4
$-CO_2H$	$-C_6H_5SO2NH_3$	H
$-CO_2CH_3$	$-C_6H_5SO2NH_3$	H
$-CO_2C_2H_5$	$-C_6H_5SO2NH_3$	H
$-CONH_2$	$-C_6H_5SO2NH_3$	H
$-CONHCH_3$	$-C_6H_5SO2NH_3$	H
$-CONH(C_6H_3)$	$-C_6H_5SO2NH_3$	H
$-CON(CH_3)_2$	$-C_6H_5SO2NH_3$	H
$-CON(C_2H_5)_2$	$-C_6H_5SO2NH_3$	H
$-CON(CH_3)(C_2H_5)$	$-C_6H_5SO2NH_3$	H
$-CON(CH_3)(C_6H_5)$	$-C_6H_5SO2NH_3$	H
	$-C_6H_5SO2NH_3$	H
	$-C_6H_5SO2NH_3$	H
-CN	$-C_6H_5SO2NH_3$	H
$-CH_2OH$	$-C_6H_5SO2NH_3$	H
$-CH_2OCH_3$	$-C_6H_5SO2NH_3$	H
$-CH_2OC_2H_5$	$-C_6H_5SO2NH_3$	H
$-CH_2OC_6H_5$	$-C_6H_5SO2NH_3$	H
$-CH_2SCH_3$	$-C_6H_5SO2NH_3$	H
$-CH_2SC_2H_5$	$-C_6H_5SO2NH_3$	H
$-CH_2SC_6H_5$	$-C_6H_5SO2NH_3$	H
$-CH_2SOCH_3$	$-C_6H_5SO2NH_3$	H
$-CH_2SOC_2H_5$	$-C_6H_5SO2NH_3$	H
$-CH_2SOC_6H_5$	$-C_6H_5SO2NH_3$	H
$-CH_2SO_2CH_3$	$-C_6H_5SO2NH_3$	H
$-CH_2SO_2C_2H_5$	$-C_6H_5SO2NH_3$	H
$-CH_2SO_2C_6H_5$	$-C_6H_5SO2NH_3$	H
$-CF_3$	$-C_6H_5SO2NH_3$	6-F
$-CF_3$	$-C_6H_5SO2NH_3$	7-F

TABLE VII (cont.)

General Structure Ig

R^1	R^2	R^4
$-CF_3$	$-C_6H_5SO2NH_3$	8-F
$-CF_3$	$-C_6H_5SO2NH_3$	7-Cl
$-CF_3$	$-C_6H_5SO2NH_3$	8-Cl
$-CF_3$	$-C_6H_5SO2NH_3$	7,8-(OCH2O)-
$-CF_3$	$-C_6H_5SO2NH_3$	7-N(CH3)2
$-CF_3$	$-C_6H_5SO2NH_3$	7-OCH3
$-CF_3$	$-C_6H_5SO2NH_3$	6-F, 7-OCH3
$-CF_3$	$-C_6H_5SO2NH_3$	6-Cl, 7-OCH3
$-CF_3$	$-C_6H_5SO2NH_3$	7-Cl, 6-F
$-CF_3$	$-C_6H_5SO2NH_3$	7-CH3
$-CF_3$	$-C_6H_5SO2NH_3$	6-F, 7-CH3
$-CF_3$	$-C_6H_5SO2NH_3$	6,7-F
$-CF_3$	$-C_6H_5SO2NH_3$	7-SCH3
$-CF_3$	$-C_6H_5SO2NH_3$	6-F, 7-SCH3
$-CF_3$	$-C_6H_5SO2NH_3$	7-SOCH3
$-CF_3$	$-C_6H_5SO2NH_3$	6-F, 7-SOCH3
$-CF_3$	$-C_6H_5SO2NH_3$	6-F, 7-CH3
$-CF_3$	-thienylSO_2NH_2	6-F, 7-OCH_3
$-CF_3$	$-C_6H_5F$	7-SO2NH2
$-CF_3$	$-C_6H_5Cl$	7-SO2NH2
$-CF_3$	$-C_6H_5OCH3$	7-SO2NH2
$-CF_3$	$-C_6H_5CH3$	7-SO2NH2
$-CF_3$	$-C_6H_5SOCH3$	7-SO2NH2

TABLE VIII

General Structure Ih

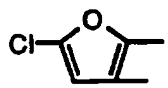
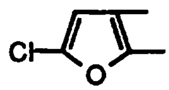
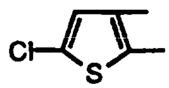
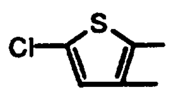
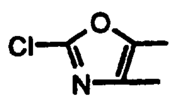
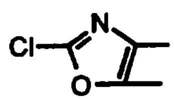
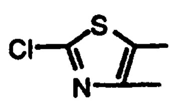
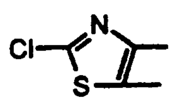
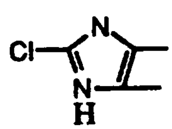
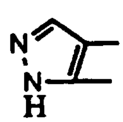
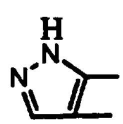
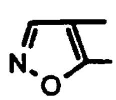
B	R^2
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$

TABLE VIII (cont.)

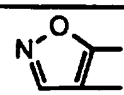
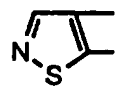
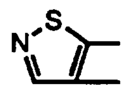
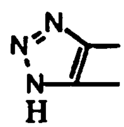
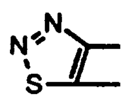
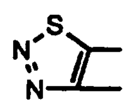
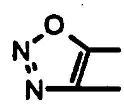
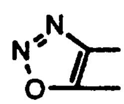
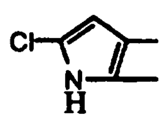
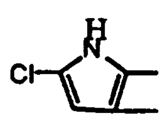
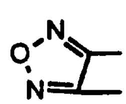
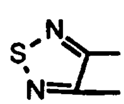
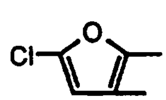
B	R^2
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2NH_2$

TABLE VIII (cont.)

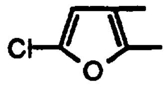
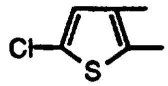
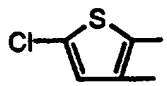
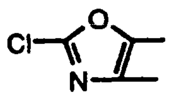
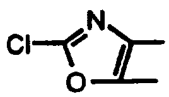
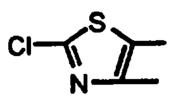
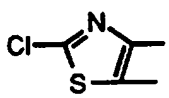
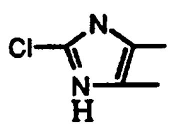
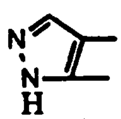
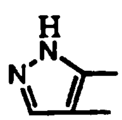
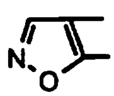
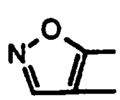
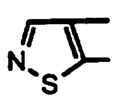
B	R^2
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$

TABLE VIII (cont.)

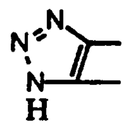
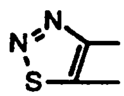
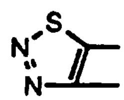
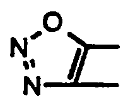
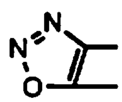
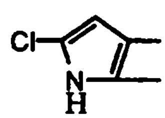
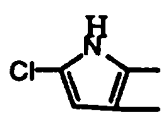
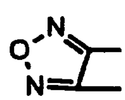
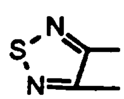
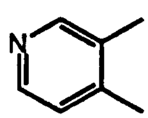
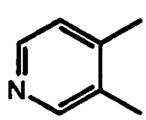
B	R^2
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$

TABLE IX

General Structure Ii

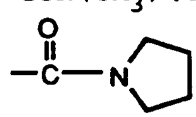
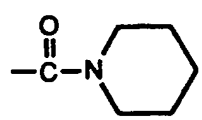
p	R^1	R^2	R^4
0	$-CF_3$	$-C_6H_5SO_2CH_3$	H
0	$-CF_2H$	$-C_6H_5SO_2CH_3$	H
0	$-CF_2Cl$	$-C_6H_5SO_2CH_3$	H
0	$-CF_2CF_3$	$-C_6H_5SO_2CH_3$	H
0	$-CO_2H$	$-C_6H_5SO_2CH_3$	H
0	$-CO_2CH_3$	$-C_6H_5SO_2CH_3$	H
0	$-CO_2C_2H_5$	$-C_6H_5SO_2CH_3$	H
0	$-CONH_2$	$-C_6H_5SO_2CH_3$	H
0	$-CONHCH_3$	$-C_6H_5SO_2CH_3$	H
0	$-CONH(C_6H_3)$	$-C_6H_5SO_2CH_3$	H
0	$-CON(CH_3)_2$	$-C_6H_5SO_2CH_3$	H
0	$-CON(C_2H_5)_2$	$-C_6H_5SO_2CH_3$	H
0	$-CON(CH_3)(C_2H_5)$	$-C_6H_5SO_2CH_3$	H
0	$-CON(CH_3)(C_6H_5)$	$-C_6H_5SO_2CH_3$	H
0		$-C_6H_5SO_2CH_3$	H
0		$-C_6H_5SO_2CH_3$	H
0	$-CN$	$-C_6H_5SO_2CH_3$	H
0	$-CH_2OH$	$-C_6H_5SO_2CH_3$	H
0	$-CH_2OCH_3$	$-C_6H_5SO_2CH_3$	H
0	$-CH_2OC_2H_5$	$-C_6H_5SO_2CH_3$	H
0	$-CH_2OC_6H_5$	$-C_6H_5SO_2CH_3$	H
0	$-CH_2SCH_3$	$-C_6H_5SO_2CH_3$	H
0	$-CH_2SC_2H_5$	$-C_6H_5SO_2CH_3$	H
0	$-CH_2SC_6H_5$	$-C_6H_5SO_2CH_3$	H
0	$-CH_2SOCH_3$	$-C_6H_5SO_2CH_3$	H
0	$-CH_2SOC_2H_5$	$-C_6H_5SO_2CH_3$	H
0	$-CH_2SOC_6H_5$	$-C_6H_5SO_2CH_3$	H
0	$-CH_2SO_2CH_3$	$-C_6H_5SO_2CH_3$	H

TABLE IX (cont.)

General Structure Ii

p	R^1	R^2	R^4
0	$-CH_2SO_2C_2H_5$	$-C_6H_5SO_2CH_3$	H
0	$-CH_2SO_2C_6H_5$	$-C_6H_5SO_2CH_3$	H
0	$-CF_3$	$-C_6H_5SO_2CH_3$	6-F
0	$-CF_3$	$-C_6H_5SO_2CH_3$	7-F
0	$-CF_3$	$-C_6H_5SO_2CH_3$	8-F
0	$-CF_3$	$-C_6H_5SO_2CH_3$	7-Cl
0	$-CF_3$	$-C_6H_5SO_2CH_3$	8-Cl
0	$-CF_3$	$-C_6H_5SO_2CH_3$	7,8-(OCH2O)-
0	$-CF_3$	$-C_6H_5SO_2CH_3$	7-N(CH3)2
0	$-CF_3$	$-C_6H_5SO_2CH_3$	7-OCH3
0	$-CF_3$	$-C_6H_5SO_2CH_3$	6-F, 7-OCH3
0	$-CF_3$	$-C_6H_5SO_2CH_3$	6-Cl, 7-OCH3
0	$-CF_3$	$-C_6H_5SO_2CH_3$	7-Cl, 6-F
0	$-CF_3$	$-C_6H_5SO_2CH_3$	7-CH3
0	$-CF_3$	$-C_6H_5SO_2CH_3$	6-F, 7-CH3
0	$-CF_3$	$-C_6H_5SO_2CH_3$	6,7-F
0	$-CF_3$	$-C_6H_5SO_2CH_3$	7-SCH3
0	$-CF_3$	$-C_6H_5SO_2CH_3$	6-F, 7-SCH3
0	$-CF_3$	$-C_6H_5SO_2CH_3$	7-SOCH3
0	$-CF_3$	$-C_6H_5SO_2CH_3$	6-F, 7-SOCH3
0	$-CF_3$	$-C_6H_5SO_2CH_3$	6-F, 7-CH3
0	$-CF_3$	$-C_6H_5F$	7-SO2CH3
0	$-CF_3$	$-C_6H_5Cl$	7-SO2CH3
0	$-CF_3$	$-C_6H_5OCH3$	7-SO2CH3
0	$-CF_3$	$-C_6H_5CH3$	7-SO2CH3
0	$-CF_3$	$-C_6H_5SOCH3$	7-SO2CH3
0	$-CF_3$	$-C_6H_5SO2NH2$	H
0	$-CF_2H$	$-C_6H_5SO2NH2$	H
0	$-CF_2H$	$-C_6H_5SO2NH2$	7-F
0	$-CF_2H$	$-C_6H_5SO2NH2$	7-CH3
0	$-CF_2H$	$-C_6H_5SO2NH2$	7-Cl
0	$-CF_2Cl$	$-C_6H_5SO2NH2$	H

TABLE IX (cont.)

General Structure Ii

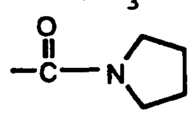
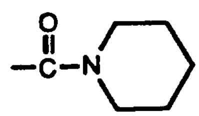
p	R^1	R^2	R^4
0	$-CF_2CF_3$	$-C_6H_5SO2NH2$	H
0	$-CO_2H$	$-C_6H_5SO2NH2$	H
0	$-CO_2CH_3$	$-C_6H_5SO2NH2$	H
0	$-CO_2C_2H_5$	$-C_6H_5SO2NH2$	H
0	$-CONH_2$	$-C_6H_5SO2NH2$	H
0	$-CONHCH_3$	$-C_6H_5SO2NH2$	H
0	$-CONH(C_6H_3)$	$-C_6H_5SO2NH2$	H
0	$-CON(CH_3)_2$	$-C_6H_5SO2NH2$	H
0	$-CON(C_2H_5)_2$	$-C_6H_5SO2NH2$	H
0	$-CON(CH_3)(C_2H_5)$	$-C_6H_5SO2NH2$	H
0	$-CON(CH_3)(C_6H_5)$	$-C_6H_5SO2NH2$	H
0		$-C_6H_5SO2NH2$	H
0		$-C_6H_5SO2NH2$	H
0	$-CN$	$-C_6H_5SO2NH2$	H
0	$-CN$	$-C_6H_5SO2NH2$	7-F
0	$-CN$	$-C_6H_5SO2NCHN(CH3)2$	7-F
0	$-CH_2OH$	$-C_6H_5SO2NH2$	H
0	$-CH_2OH$	$-C_6H_5SO2NH2$	7-F
0	$-CH_2OCH_3$	$-C_6H_5SO2NH2$	H
0	$-CH_2OC_2H_5$	$-C_6H_5SO2NH2$	H
0	$-CH_2OC_6H_5$	$-C_6H_5SO2NH2$	H
0	$-CH_2SCH_3$	$-C_6H_5SO2NH2$	H
0	$-CH_2SC_2H_5$	$-C_6H_5SO2NH2$	H
0	$-CH_2SC_6H_5$	$-C_6H_5SO2NH2$	H
0	$-CH_2SOCH_3$	$-C_6H_5SO2NH2$	H
0	$-CH_2SOC_2H_5$	$-C_6H_5SO2NH2$	H
0	$-CH2SOC6H5$	$-C_6H_5SO2NH2$	H
0	$-CH_2SO_2CH_3$	$-C_6H_5SO2NH2$	H

TABLE IX (cont.)

General Structure Ii

p	R^1	R^2	R^4
0	$-CH_2SO_2C_2H_5$	$-C_6H_5SO2NH2$	H
0	$-CH_2SO_2C_6H_5$	$-C_6H_5SO2NH2$	H
0	$-CONH_2$	$-C_6H_5SO2NH2$	7-F
0	$-CO_2CH_3$	$-C_6H_5SO2NH2$	7-F
0	$-CF_3$	$-C_6H_5SO2NH2$	6-F
0	$-CF_3$	$-C_6H_5SO2NH2$	7-F
0	$-CF_3$	$-C_6H_5SO2NH2$	8-F
0	$-CF_3$	$-C_6H_5SO2NH2$	7-Cl
0	$-CF_3$	$-C_6H_5SO2NH2$	8-Cl
0	$-CF_3$	$-C_6H_5SO2NH2$	7,8-(OCH2O)-
0	$-CF_3$	$-C_6H_5SO2NH2$	6,7-(OCH2O)-
0	$-CF_3$	$-C_6H_5SO2NH2$	7-N(CH3)2
0	$-CF_3$	$-C_6H_5SO2NH2$	7-OCH3
0	$-CF_3$	$-C_6H_5SO2NH2$	6-F, 7-OCH3
0	$-CF_3$	$-C_6H_5SO2NH2$	6,8-F, 7-OCH3
0	$-CF_3$	$-C_6H_5SO2NH2$	6-Cl, 7-OCH3
0	$-CF_3$	$-C_6H_5SO2NH2$	7-Cl, 6-F
0	$-CF_3$	$-C_6H_5SO2NH2$	7-CH3
0	$-CF_3$	$-C_6H_5SO2NH2$	6-F, 7-CH3
0	$-CF_3$	$-C_6H_5SO2NH2$	6,7-F
0	$-CF_3$	$-C_6H_5SO2NH2$	7-SCH3
0	$-CF_3$	$-C_6H_5SO2NH2$	6-F, 7-SCH3
0	$-CF_3$	$-C_6H_5SO2NH2$	7-SOCH3
0	$-CF_3$	$-C_6H_5SO2NH2$	6-F, 7-SOCH3
0	$-CF_3$	$-C_6H_5SO2NH2$	6-Cl, 7-CH3
0	$-CF_3$	thienylSO_2NH_2	6-F, 7-OCH_3
0	$-CF_3$	$-C_6H_5F$	7-SO2NH2
0	$-CF_3$	$-C_6H_5Cl$	7-SO2NH2
0	$-CF_3$	$-C_6H_5OCH3$	7-SO2NH2
0	$-CF_3$	$-C_6H_5CH3$	7-SO2NH2
0	$-CF_3$	$-C_6H_5SOCH3$	7-SO2NH2
0	$-CHF_2$	$-C_6H_5SO2NH2$	6-F, 7-OCH3

TABLE IX (cont.)

General Structure Ii

p	R^1	R^2	R^4
1	$-CF_3$	$-C_6H_5SO2NH2$	6-F, 7-OCH3
1	$-CF_3$	$-C_6H_5SO2NH2$	6-Cl, 7-OCH3
1	$-CF_3$	$-C_6H_5SO2NH2$	7-Cl, 6-F
1	$-CF_3$	$-C_6H_5SO2NH2$	6-F, 7-CH3
1	$-CF_3$	$-C_6H_5SO2NH2$	6,7-F
1	$-CF_3$	$-C_6H_5SO2NH2$	6-F, 7-SCH3
1	$-CF_3$	$-C_6H_5SO2NH2$	6-F, 7-SOCH3
1	$-CF_3$	$-C_6H_5SO2NH2$	6-Cl, 7-CH3

TABLE X

General Structure Ij

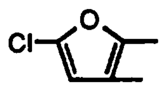
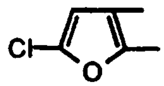
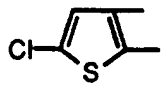
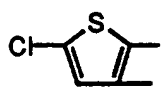
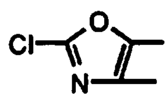
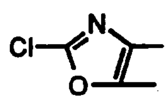
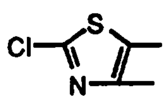
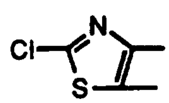
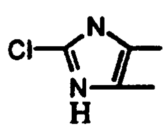
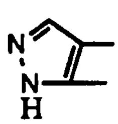
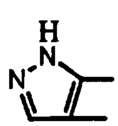
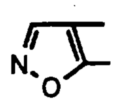
B	R^2	p
	$-C_6H_5SO2CH2$	0
	$-C_6H_5SO2CH2$	0
	$-C_6H_5SO2CH2$	0
	$-C_6H_5SO2CH2$	0
	$-C_6H_5SO2CH2$	0
	$-C_6H_5SO2CH2$	0
	$-C_6H_5SO2CH2$	0
	$-C_6H_5SO2CH2$	0
	$-C_6H_5SO2CH2$	0
	$-C_6H_5SO2CH2$	0
	$-C_6H_5SO2CH2$	0
	$-C_6H_5SO2CH2$	0

TABLE X (cont.)

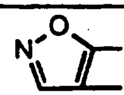
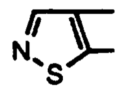
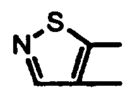
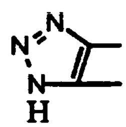
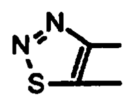
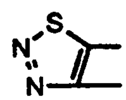
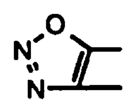
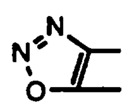
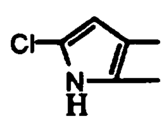
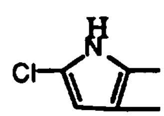
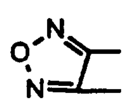
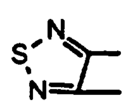
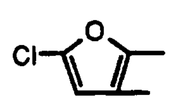
B	R^2	p
	$-C_6H_5SO_2CH_2$	0
	$-C_6H_5SO_2CH_2$	0
	$-C_6H_5SO_2CH_2$	0
	$-C_6H_5SO_2CH_2$	0
	$-C_6H_5SO_2CH_2$	0
	$-C_6H_5SO_2CH_2$	0
	$-C_6H_5SO_2CH_2$	0
	$-C_6H_5SO_2CH_2$	0
	$-C_6H_5SO_2CH_2$	0
	$-C_6H_5SO_2CH_2$	0
	$-C_6H_5SO_2CH_2$	0
	$-C_6H_5SO_2CH_2$	0
	$-C_6H_5SO_2NH_2$	0

TABLE X (cont.)

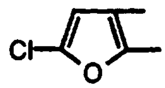
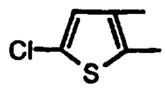
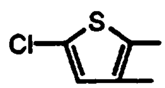
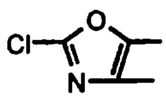
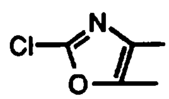
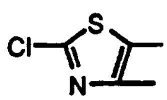
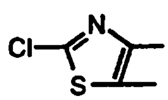
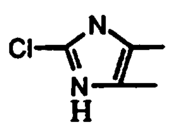
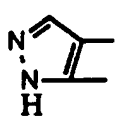
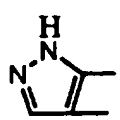
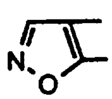
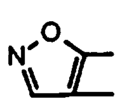
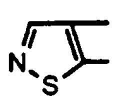
B	R^2	p
	$-C_6H_5$SO2NH2	0
	$-C_6H_5$SO2NH2	0
	$-C_6H_5$SO2NH2	0
	$-C_6H_5$SO2NH2	0
	$-C_6H_5$SO2NH2	0
	$-C_6H_5$SO2NH2	0
	$-C_6H_5$SO2NH2	0
	$-C_6H_5$SO2NH2	0
	$-C_6H_5$SO2NH2	0
	$-C_6H_5$SO2NH2	0
	$-C_6H_5$SO2NH2	0
	$-C_6H_5$SO2NH2	0
	$-C_6H_5$SO2NH2	0

TABLE X (cont.)

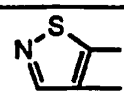
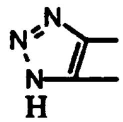
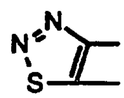
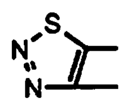
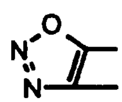
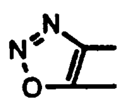
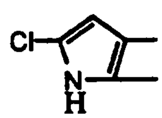
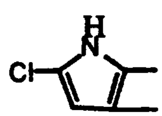
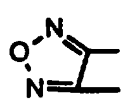
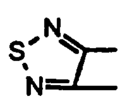
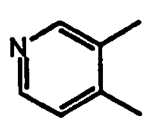
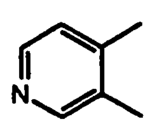
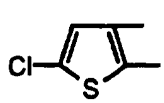
B	R^2	p
	$-C_6H_5SO_2NH_2$	0
	$-C_6H_5SO_2NH_2$	0
	$-C_6H_5SO_2NH_2$	0
	$-C_6H_5SO_2NH_2$	0
	$-C_6H_5SO_2NH_2$	0
	$-C_6H_5SO_2NH_2$	0
	$-C_6H_5SO_2NH_2$	0
	$-C_6H_5SO_2NH_2$	0
	$-C_6H_5SO_2NH_2$	0
	$-C_6H_5SO_2NH_2$	0
	$-C_6H_5SO_2NH_2$	0
	$-C_6H_5SO_2NH_2$	0
	$-C_6H_5SO_2NH_2$	1

TABLE XI

General Structure Ik

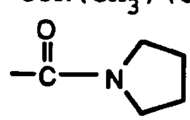
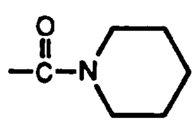
p	R^1	R^2	R^4
0	$-CF_3$	$-C_6H_5SO2CH_3$	H
0	$-CF_2H$	$-C_6H_5SO2CH_3$	H
0	$-CF_2Cl$	$-C_6H_5SO2CH_3$	H
0	$-CF_2CF_3$	$-C_6H_5SO2CH_3$	H
0	$-CO_2H$	$-C_6H_5SO2CH_3$	H
0	$-CO_2CH_3$	$-C_6H_5SO2CH_3$	H
0	$-CO_2C_2H_5$	$-C_6H_5SO2CH_3$	H
0	$-CONH_2$	$-C_6H_5SO2CH_3$	H
0	$-CONHCH_3$	$-C_6H_5SO2CH_3$	H
0	$-CONH(C_6H_3)$	$-C_6H_5SO2CH_3$	H
0	$-CON(CH_3)_2$	$-C_6H_5SO2CH_3$	H
0	$-CON(C_2H_5)_2$	$-C_6H_5SO2CH_3$	H
0	$-CON(CH_3)(C_2H_5)$	$-C_6H_5SO2CH_3$	H
0	$-CON(CH_3)(C_6H_5)$	$-C_6H_5SO2CH_3$	H
0		$-C_6H_5SO2CH_3$	H
0		$-C_6H_5SO2CH_3$	H
0	$-CN$	$-C_6H_5SO2CH_3$	H
0	$-CH_2OH$	$-C_6H_5SO2CH_3$	H
0	$-CH_2OCH_3$	$-C_6H_5SO2CH_3$	H
0	$-CH_2OC_2H_5$	$-C_6H_5SO2CH_3$	H
0	$-CH_2OC_6H_5$	$-C_6H_5SO2CH_3$	H
0	$-CH_2SCH_3$	$-C_6H_5SO2CH_3$	H
0	$-CH_2SC_2H_5$	$-C_6H_5SO2CH_3$	H
0	$-CH_2SC_6H_5$	$-C_6H_5SO2CH_3$	H
0	$-CH_2SOCH_3$	$-C_6H_5SO2CH_3$	H
0	$-CH_2SOC_2H_5$	$-C_6H_5SO2CH_3$	H
0	$-CH2SOC6H5$	$-C_6H_5SO2CH_3$	H
0	$-CH_2SO_2CH_3$	$-C_6H_5SO2CH_3$	H

TABLE XI (cont.)

General Structure Ik

p	R^1	R^2	R^4
0	$-CH_2SO_2C_2H_5$	$-C_6H_5SO2CH_3$	H
0	$-CH_2SO_2C_6H_5$	$-C_6H_5SO2CH_3$	H
0	$-CF_3$	$-C_6H_5SO2CH_3$	6-F
0	$-CF_3$	$-C_6H_5SO2CH_3$	7-F
0	$-CF_3$	$-C_6H_5SO2CH_3$	8-F
0	$-CF_3$	$-C_6H_5SO2CH_3$	7-Cl
0	$-CF_3$	$-C_6H_5SO2CH_3$	8-Cl
0	$-CF_3$	$-C_6H_5SO2CH_3$	7,8-(OCH2O)-
0	$-CF_3$	$-C_6H_5SO2CH_3$	7-N(CH3)2
0	$-CF_3$	$-C_6H_5SO2CH_3$	7-OCH3
0	$-CF_3$	$-C_6H_5SO2CH_3$	6-F, 7-OCH3
0	$-CF_3$	$-C_6H_5SO2CH_3$	6-Cl, 7-OCH3
0	$-CF_3$	$-C_6H_5SO2CH_3$	7-Cl, 6-F
0	$-CF_3$	$-C_6H_5SO2CH_3$	7-CH3
0	$-CF_3$	$-C_6H_5SO2CH_3$	6-F, 7-CH3
0	$-CF_3$	$-C_6H_5SO2CH_3$	6,7-F
0	$-CF_3$	$-C_6H_5SO2CH_3$	7-SCH3
0	$-CF_3$	$-C_6H_5SO2CH_3$	6-F, 7-SCH3
0	$-CF_3$	$-C_6H_5SO2CH_3$	7-SOCH3
0	$-CF_3$	$-C_6H_5SO2CH_3$	6-F, 7-SOCH3
0	$-CF_3$	$-C_6H_5SO2CH_3$	6-F, 7-CH3
0	$-CF_3$	$-C_6H_5F$	7-SO2CH3
0	$-CF_3$	$-C_6H_5Cl$	7-SO2CH3
0	$-CF_3$	$-C_6H_5OCH3$	7-SO2CH3
0	$-CF_3$	$-C_6H_5CH3$	7-SO2CH3
0	$-CF_3$	$-C_6H_5SOCH3$	7-SO2CH3
0	$-CF_3$	$-C_6H_5SO2NH2$	H
0	$-CF_2H$	$-C_6H_5SO2NH2$	H
0	$-CF_2Cl$	$-C_6H_5SO2NH2$	H
0	$-CF_2CF_3$	$-C_6H_5SO2NH2$	H
0	CO_2H	$-C_6H_5SO2NH2$	H
0	$-CO_2CH_3$	$-C_6H_5SO2NH2$	H

TABLE XI (cont.)

General Structure Ik

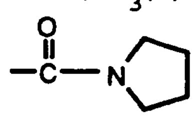
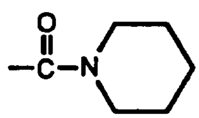
p	R^1	R^2	R^4
0	$-CO_2C_2H_5$	$-C_6H_5$SO2NH2	H
0	$-CONH_2$	$-C_6H_5$SO2NH2	H
0	$-CONHCH_3$	$-C_6H_5$SO2NH2	H
0	$-CONH(C_6H_3)$	$-C_6H_5$SO2NH2	H
0	$-CON(CH_3)_2$	$-C_6H_5$SO2NH2	H
0	$-CON(C_2H_5)_2$	$-C_6H_5$SO2NH2	H
0	$-CON(CH_3)(C_2H_5)$	$-C_6H_5$SO2NH2	H
0	$-CON(CH_3)(C_6H_5)$	$-C_6H_5$SO2NH2	H
0		$-C_6H_5$SO2NH2	H
0		$-C_6H_5$SO2NH2	H
0	-CN	$-C_6H_5$SO2NH2	H
0	$-CH_2OH$	$-C_6H_5$SO2NH2	H
0	$-CH_2OCH_3$	$-C_6H_5$SO2NH2	H
0	$-CH_2OC_2H_5$	$-C_6H_5$SO2NH2	H
0	$-CH_2OC_6H_5$	$-C_6H_5$SO2NH2	H
0	$-CH_2SCH_3$	$-C_6H_5$SO2NH2	H
0	$-CH_2SC_2H_5$	$-C_6H_5$SO2NH2	H
0	$-CH_2SC_6H_5$	$-C_6H_5$SO2NH2	H
0	$-CH_2SOCH_3$	$-C_6H_5$SO2NH2	H
0	$-CH_2SOC_2H_5$	$-C_6H_5$SO2NH2	H
0	-CH2SOC6H5	$-C_6H_5$SO2NH2	H
0	$-CH_2SO_2CH_3$	$-C_6H_5$SO2NH2	H
0	$-CH_2SO_2C_2H_5$	$-C_6H_5$SO2NH2	H
0	$-CH_2SO_2C_6H_5$	$-C_6H_5$SO2NH2	H
0	$-CF_3$	$-C_6H_5$SO2NH2	6-F
0	$-CF_3$	$-C_6H_5$SO2NH2	7-F
0	$-CF_3$	$-C_6H_5$SO2NH2	8-F
0	$-CF_3$	$-C_6H_5$SO2NH2	7-Cl

TABLE XI (cont.)

General Structure Ik

p	R^1	R^2	R^4
0	$-CF_3$	$-C_6H_5SO_2NH_2$	8-Cl
0	$-CF_3$	$-C_6H_5SO_2NH_2$	7,8-(OCH_2O)-
0	$-CF_3$	$-C_6H_5SO_2NH_2$	7-$N(CH_3)_2$
0	$-CF_3$	$-C_6H_5SO_2NH_2$	7-OCH_3
0	$-CF_3$	$-C_6H_5SO_2NH_2$	7,8-OCH_3
0	$-CF_3$	$-C_6H_5SO_2NH_2$	6-F, 7-OCH_3
0	$-CF_3$	$-C_6H_5SO_2NH_2$	6-Cl, 7-OCH_3
0	$-CF_3$	$-C_6H_5SO_2NH_2$	7-Cl, 6-F
0	$-CF_3$	$-C_6H_5SO_2NH_2$	6-$CH(CH_3)_2$
0	$-CF_3$	$-C_6H_5SO_2NH_2$	7-CH_3
0	$-CF_3$	$-C_6H_5SO_2NH_2$	6-F, 7-CH_3
0	$-CF_3$	$-C_6H_5SO_2NH_2$	6,7-F
0	$-CF_3$	$-C_6H_5SO_2NH_2$	6,7-Cl
0	$-CF_3$	$-C_6H_5SO_2NH_2$	7-SCH_3
0	$-CF_3$	$-C_6H_5SO_2NH_2$	6-F, 7-SCH_3
0	$-CF_3$	$-C_6H_5SO_2NH_2$	7-$SOCH_3$
0	$-CF_3$	$-C_6H_5SO_2NH_2$	6-F, 7-$SOCH_3$
0	$-CF_3$	$-C_6H_5SO_2NH_2$	6-Cl, 7-CH_3
0	$-CF_3$	-thienylSO_2NH_2	6-F, 7-OCH_3
0	$-CF_3$	$-C_6H_5F$	7-SO_2NH_2
0	$-CF_3$	$-C_6H_5Cl$	7-SO_2NH_2
0	$-CF_3$	$-C_6H_5OCH_3$	7-SO_2NH_2
0	$-CF_3$	$-C_6H_5CH_3$	7-SO_2NH_2
0	$-CF_3$	$-C_6H_5SOCH_3$	7-SO_2NH_2
1	$-CF_3$	$-C_6H_5SO_2NH_2$	6-F, 7-OCH_3
1	$-CF_3$	$-C_6H_5SO_2NH_2$	6-Cl, 7-OCH_3
1	$-CF_3$	$-C_6H_5SO_2NH_2$	7-Cl, 6-F
1	$-CF_3$	$-C_6H_5SO_2NH_2$	6-F, 7-CH_3
1	$-CF_3$	$-C_6H_5SO_2NH_2$	6,7-F
1	$-CF_3$	$-C_6H_5SO_2NH_2$	6-F, 7-SCH_3
1	$-CF_3$	$-C_6H_5SO_2NH_2$	6-F, 7-$SOCH_3$
1	$-CF_3$	$-C_6H_5SO_2NH_2$	6-Cl, 7-CH_3

TABLE XII

General Structure Il

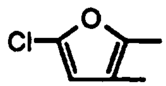
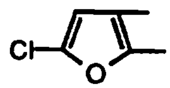
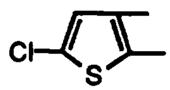
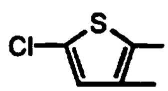
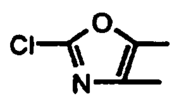
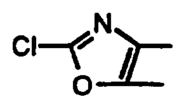
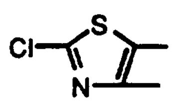
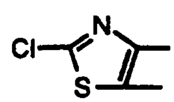
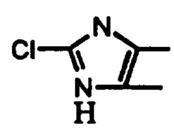
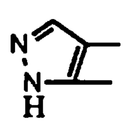
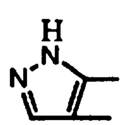
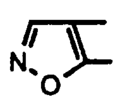
B	R^2	p
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0

TABLE XII (cont.)

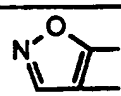
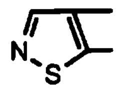
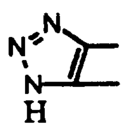
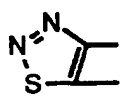
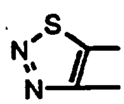
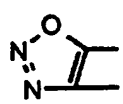
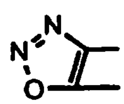
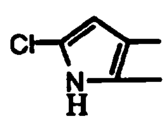
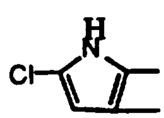
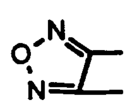
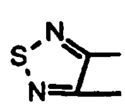
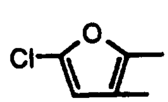
B	R^2	P
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2CH_3$	0
	$-C_6H_5SO_2NH_3$	0

TABLE XII (cont.)

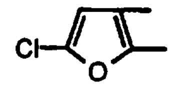
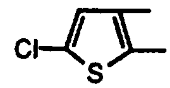
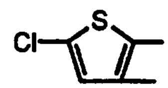
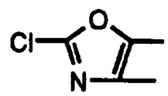
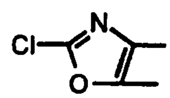
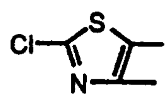
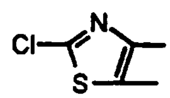
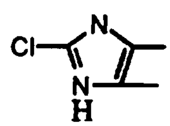
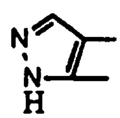
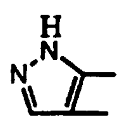
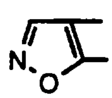
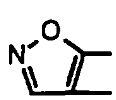
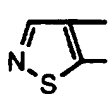
B	R^2	p
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0

TABLE XII (cont.)

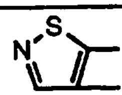
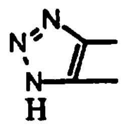
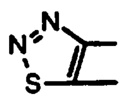
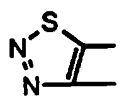
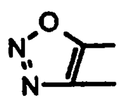
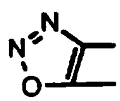
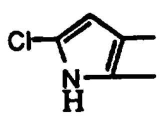
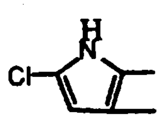
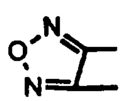
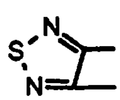
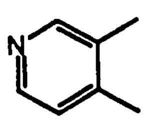
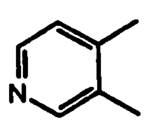
B	R^2	p
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_3$	0
	$-C_6H_5SO_2NH_2$	0
	$-C_6H_5SO_2NH_2$	0

TABLE XIII

General Structure Im

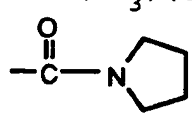
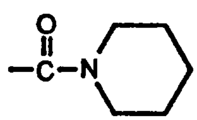
R^1	R^2	R^4
$-CF_3$	$-C_6H_5SO_2CH_3$	H
$-CF_2H$	$-C_6H_5SO_2CH_3$	H
$-CF_2Cl$	$-C_6H_5SO_2CH_3$	H
$-CF_2CF_3$	$-C_6H_5SO_2CH_3$	H
$-CO_2H$	$-C_6H_5SO_2CH_3$	H
$-CO_2CH_3$	$-C_6H_5SO_2CH_3$	H
$-CO_2C_2H_5$	$-C_6H_5SO_2CH_3$	H
$-CONH_2$	$-C_6H_5SO_2CH_3$	H
$-CONHCH_3$	$-C_6H_5SO_2CH_3$	H
$-CONH(C_6H_3)$	$-C_6H_5SO_2CH_3$	H
$-CON(CH_3)_2$	$-C_6H_5SO_2CH_3$	H
$-CON(C_2H_5)_2$	$-C_6H_5SO_2CH_3$	H
$-CON(CH_3)(C_2H_5)$	$-C_6H_5SO_2CH_3$	H
$-CON(CH_3)(C_6H_5)$	$-C_6H_5SO_2CH_3$	H
	$-C_6H_5SO_2CH_3$	H
	$-C_6H_5SO_2CH_3$	H
$-CN$	$-C_6H_5SO_2CH_3$	H
$-CH_2OH$	$-C_6H_5SO_2CH_3$	H
$-CH_2OCH_3$	$-C_6H_5SO_2CH_3$	H
$-CH_2OC_2H_5$	$-C_6H_5SO_2CH_3$	H
$-CH_2OC_6H_5$	$-C_6H_5SO_2CH_3$	H
$-CH_2SCH_3$	$-C_6H_5SO_2CH_3$	H
$-CH_2SC_2H_5$	$-C_6H_5SO_2CH_3$	H
$-CH_2SC_6H_5$	$-C_6H_5SO_2CH_3$	H
$-CH_2SOCH_3$	$-C_6H_5SO_2CH_3$	H
$-CH_2SOC_2H_5$	$-C_6H_5SO_2CH_3$	H
$-CH_2SOC_6H_5$	$-C_6H_5SO_2CH_3$	H

TABLE XIII (cont.)

General Structure Im

R^1	R^2	R^4
$-CH_2SO_2CH_3$	$-C_6H_5SO_2CH_3$	H
$-CH_2SO_2C_2H_5$	$-C_6H_5SO_2CH_3$	H
$-CH_2SO_2C_6H_5$	$-C_6H_5SO_2CH_3$	H
$-CF_3$	$-C_6H_5SO_2CH_3$	7-F
$-CF_3$	$-C_6H_5SO_2CH_3$	8-F
$-CF_3$	$-C_6H_5SO_2CH_3$	9-F
$-CF_3$	$-C_6H_5SO_2CH_3$	8-Cl
$-CF_3$	$-C_6H_5SO_2CH_3$	9-Cl
$-CF_3$	$-C_6H_5SO_2CH_3$	8,9-(OCH2O)-
$-CF_3$	$-C_6H_5SO_2CH_3$	8-N(CH3)2
$-CF_3$	$-C_6H_5SO_2CH_3$	8-OCH3
$-CF_3$	$-C_6H_5SO_2CH_3$	7-F, 8-OCH3
$-CF_3$	$-C_6H_5SO_2CH_3$	7-Cl, 8-OCH3
$-CF_3$	$-C_6H_5SO_2CH_3$	8-Cl, 7-F
$-CF_3$	$-C_6H_5SO_2CH_3$	8-CH3
$-CF_3$	$-C_6H_5SO_2CH_3$	7-F, 8-CH3
$-CF_3$	$-C_6H_5SO_2CH_3$	7,8-F
$-CF_3$	$-C_6H_5SO_2CH_3$	8-SCH3
$-CF_3$	$-C_6H_5SO_2CH_3$	7-F, 8-SCH3
$-CF_3$	$-C_6H_5SO_2CH_3$	8-SOCH3
$-CF_3$	$-C_6H_5SO_2CH_3$	7-F, 8-SOCH3
$-CF_3$	$-C_6H_5SO_2CH_3$	7-F, 8-CH3
$-CF_3$	$-C_6H_5F$	8-SO2CH3
$-CF_3$	$-C_6H_5Cl$	8-SO2CH3
$-CF_3$	$-C_6H_5OCH3$	8-SO2CH3
$-CF_3$	$-C_6H_5CH3$	8-SO2CH3
$-CF_3$	$-C_6H_5SOCH3$	8-SO2CH3
$-CF_3$	$-C_6H_5SO2NH2$	H
$-CF_2H$	$-C_6H_5SO2NH2$	H
$-CF_2Cl$	$-C_6H_5SO2NH2$	H
$-CF_2CF_3$	$-C_6H_5SO2NH2$	H
$-CO_2H$	$-C_6H_5SO2NH2$	H

TABLE XIII (cont.)

General Structure Im

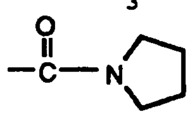
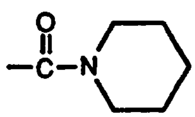
R^1	R^2	R^4
$-CO_2CH_3$	$-C_6H_5$SO2NH2	H
$-CO_2C_2H_5$	$-C_6H_5$SO2NH2	H
$-CONH_2$	$-C_6H_5$SO2NH2	H
$-CONHCH_3$	$-C_6H_5$SO2NH2	H
$-CONH(C_6H_3)$	$-C_6H_5$SO2NH2	H
$-CON(CH_3)_2$	$-C_6H_5$SO2NH2	H
$-CON(C_2H_5)_2$	$-C_6H_5$SO2NH2	H
$-CON(CH_3)(C_2H_5)$	$-C_6H_5$SO2NH2	H
$-CON(CH_3)(C_6H_5)$	$-C_6H_5$SO2NH2	H
	$-C_6H_5$SO2NH2	H
	$-C_6H_5$SO2NH2	H
-CN	$-C_6H_5$SO2NH2	H
$-CH_2OH$	$-C_6H_5$SO2NH2	H
$-CH_2OCH_3$	$-C_6H_5$SO2NH2	H
$-CH_2OC_2H_5$	$-C_6H_5$SO2NH2	H
$-CH_2OC_6H_5$	$-C_6H_5$SO2NH2	H
$-CH_2SCH_3$	$-C_6H_5$SO2NH2	H
$-CH_2SC_2H_5$	$-C_6H_5$SO2NH2	H
$-CH_2SC_6H_5$	$-C_6H_5$SO2NH2	H
$-CH_2SOCH_3$	$-C_6H_5$SO2NH2	H
$-CH_2SOC_2H_5$	$-C_6H_5$SO2NH2	H
-CH2SOC6H5	$-C_6H_5$SO2NH2	H
$-CH_2SO_2CH_3$	$-C_6H_5$SO2NH2	H
$-CH_2SO_2C_2H_5$	$-C_6H_5$SO2NH2	H
$-CH_2SO_2C_6H_5$	$-C_6H_5$SO2NH2	H
$-CF_3$	$-C_6H_5$SO2NH2	7-F
$-CF_3$	$-C_6H_5$SO2NH2	8-F

TABLE XIII (cont.)

General Structure Im

R^1	R^2	R^4
$-CF_3$	$-C_6H_5SO2NH2$	9-F
$-CF_3$	$-C_6H_5SO2NH2$	7,8-(OCH2O)-
$-CF_3$	$-C_6H_5SO2NH2$	8-N(CH3)2
$-CF_3$	$-C_6H_5SO2NH2$	8-OCH3
$-CF_3$	$-C_6H_5SO2NH2$	7-F, 8-OCH3
$-CF_3$	$-C_6H_5SO2NH2$	7-Cl, 8-OCH3
$-CF_3$	$-C_6H_5SO2NH2$	8-Cl, 7-F
$-CF_3$	$-C_6H_5SO2NH2$	8-CH3
$-CF_3$	$-C_6H_5SO2NH2$	7-F, 8-CH3
$-CF_3$	$-C_6H_5SO2NH2$	7,8-F
$-CF_3$	$-C_6H_5SO2NH2$	8-SCH3
$-CF_3$	$-C_6H_5SO2NH2$	7-F, 8-SCH3
$-CF_3$	$-C_6H_5SO2NH2$	8-SOCH3
$-CF_3$	$-C_6H_5SO2NH2$	7-F, 8-SOCH3
$-CF_3$	$-C_6H_5SO2NH2$	7-F, 8-CH3
$-CF_3$	thienylSO_2NH_2	7-F, 9OCH_3
$-CF_3$	$-C_6H_5F$	8-SO2NH2
$-CF_3$	$-C_6H_5Cl$	8-SO2NH2
$-CF_3$	$-C_6H_5OCH3$	8-SO2NH2
$-CF_3$	$-C_6H_5CH3$	8-SO2NH2
$-CF_3$	$-C_6H_5SOCH3$	8-SO2NH2
$-CF_3$	$-C_6H_5SO2NH2$	8-Cl
$-CF_3$	$-C_6H_5SO2NH2$	9-Cl

TABLE XIV

General Structure In

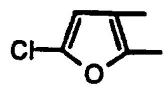
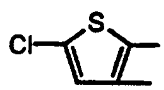
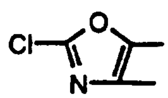
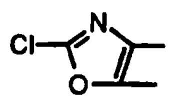
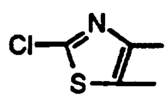
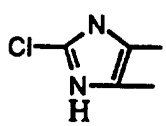
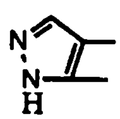
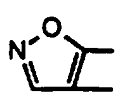
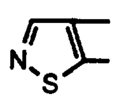
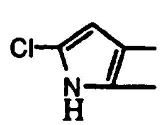
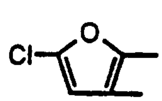
B	R^2
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2NH_2$

TABLE XIV (cont.)

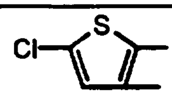
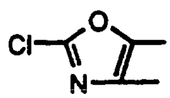
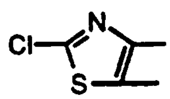
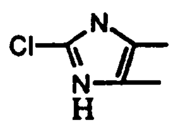
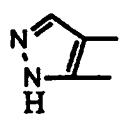
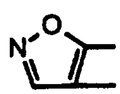
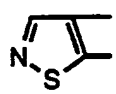
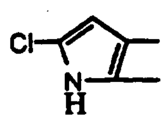
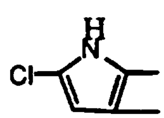
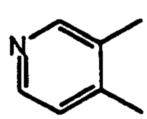
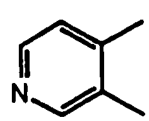
B	R^2
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$

TABLE XV

General Structure Io

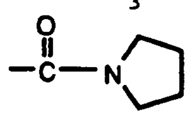
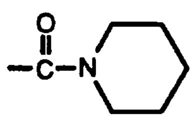
R^1	R^2	R^4
$-CF_3$	$-C_6H_5SO2CH3$	H
$-CF_2H$	$-C_6H_5SO2CH3$	H
$-CF_2Cl$	$-C_6H_5SO2CH3$	H
$-CF_2CF_3$	$-C_6H_5SO2CH3$	H
$-CO_2H$	$-C_6H_5SO2CH3$	H
$-CO_2CH_3$	$-C_6H_5SO2CH3$	H
$-CO_2C_2H_5$	$-C_6H_5SO2CH3$	H
$-CONH_2$	$-C_6H_5SO2CH3$	H
$-CONHCH_3$	$-C_6H_5SO2CH3$	H
$-CONH(C_6H_3)$	$-C_6H_5SO2CH3$	H
$-CON(CH_3)_2$	$-C_6H_5SO2CH3$	H
$-CON(C_2H_5)_2$	$-C_6H_5SO2CH3$	H
$-CON(CH_3)(C_2H_5)$	$-C_6H_5SO2CH3$	H
$-CON(CH_3)(C_6H_5)$	$-C_6H_5SO2CH3$	H
	$-C_6H_5SO2CH3$	H
	$-C_6H_5SO2CH3$	H
$-CN$	$-C_6H_5SO2CH3$	H
$-CH_2OH$	$-C_6H_5SO2CH3$	H
$-CH_2OCH_3$	$-C_6H_5SO2CH3$	H
$-CH_2OC_2H_5$	$-C_6H_5SO2CH3$	H
$-CH_2OC_6H_5$	$-C_6H_5SO2CH3$	H
$-CH_2SCH_3$	$-C_6H_5SO2CH3$	H
$-CH_2SC_2H_5$	$-C_6H_5SO2CH3$	H
$-CH_2SC_6H_5$	$-C_6H_5SO2CH3$	H
$-CH_2SOCH_3$	$-C_6H_5SO2CH3$	H
$-CH_2SOC_2H_5$	$-C_6H_5SO2CH3$	H
$-CH_2SOC_6H_5$	$-C_6H_5SO2CH3$	H
$-CH_2SO_2CH_3$	$-C_6H_5SO2CH3$	H

TABLE XV (c nt.)

General Structure Io

R^1	R^2	R^4
$-CH_2SO_2C_2H_5$	$-C_6H_5SO_2CH_3$	H
$-CH_2SO_2C_6H_5$	$-C_6H_5SO_2CH_3$	H
$-CF_3$	$-C_6H_5SO_2CH_3$	7-F
$-CF_3$	$-C_6H_5SO_2CH_3$	8-F
$-CF_3$	$-C_6H_5SO_2CH_3$	9-F
$-CF_3$	$-C_6H_5SO_2CH_3$	8-Cl
$-CF_3$	$-C_6H_5SO_2CH_3$	9-Cl
$-CF_3$	$-C_6H_5SO_2CH_3$	8,9-(OCH_2O)-
$-CF_3$	$-C_6H_5SO_2CH_3$	8-$N(CH_3)_2$
$-CF_3$	$-C_6H_5SO_2CH_3$	8-OCH_3
$-CF_3$	$-C_6H_5SO_2CH_3$	7-F, 8-OCH_3
$-CF_3$	$-C_6H_5SO_2CH_3$	7-Cl, 8-OCH_3
$-CF_3$	$-C_6H_5SO_2CH_3$	8-Cl, 7-F
$-CF_3$	$-C_6H_5SO_2CH_3$	8-CH_3
$-CF_3$	$-C_6H_5SO_2CH_3$	7-F, 8-CH_3
$-CF_3$	$-C_6H_5SO_2CH_3$	7,8-F
$-CF_3$	$-C_6H_5SO_2CH_3$	8-SCH_3
$-CF_3$	$-C_6H_5SO_2CH_3$	7-F, 8-SCH_3
$-CF_3$	$-C_6H_5SO_2CH_3$	8-$SOCH_3$
$-CF_3$	$-C_6H_5SO_2CH_3$	7-F, 8-$SOCH_3$
$-CF_3$	$-C_6H_5SO_2CH_3$	7-F, 8-CH_3
$-CF_3$	$-C_6H_5F$	8-SO_2CH_3
$-CF_3$	$-C_6H_5Cl$	8-SO_2CH_3
$-CF_3$	$-C_6H_5OCH_3$	8-SO_2CH_3
$-CF_3$	$-C_6H_5CH_3$	8-SO_2CH_3
$-CF_3$	$-C_6H_5SOCH_3$	8-SO_2CH_3
$-CF_3$	$-C_6H_5SO_2NH_2$	H
$-CF_2H$	$-C_6H_5SO_2NH_2$	H
$-CF_2Cl$	$-C_6H_5SO_2NH_2$	H
$-CF_2CF_3$	$-C_6H_5SO_2NH_2$	H
$-CO_2H$	$-C_6H_5SO_2NH_2$	H
$-CO_2CH_3$	$-C_6H_5SO_2NH_2$	H

TABLE XV (cont.)

General Structure Io

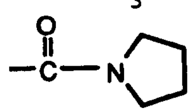
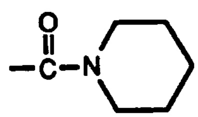
R^1	R^2	R^4
$-CO_2C_2H_5$	$-C_6H_5SO2NH2$	H
$-CONH_2$	$-C_6H_5SO2NH2$	H
$-CONHCH_3$	$-C_6H_5SO2NH2$	H
$-CONH(C_6H_3)$	$-C_6H_5SO2NH2$	H
$-CON(CH_3)_2$	$-C_6H_5SO2NH2$	H
$-CON(C_2H_5)_2$	$-C_6H_5SO2NH2$	H
$-CON(CH_3)(C_2H_5)$	$-C_6H_5SO2NH2$	H
$-CON(CH_3)(C_6H_5)$	$-C_6H_5SO2NH2$	H
	$-C_6H_5SO2NH2$	H
	$-C_6H_5SO2NH2$	H
$-CN$	$-C_6H_5SO2NH2$	H
$-CH_2OH$	$-C_6H_5SO2NH2$	H
$-CH_2OCH_3$	$-C_6H_5SO2NH2$	H
$-CH_2OC_2H_5$	$-C_6H_5SO2NH2$	H
$-CH_2OC_6H_5$	$-C_6H_5SO2NH2$	H
$-CH_2SCH_3$	$-C_6H_5SO2NH2$	H
$-CH_2SC_2H_5$	$-C_6H_5SO2NH2$	H
$-CH_2SC_6H_5$	$-C_6H_5SO2NH2$	H
$-CH_2SOCH_3$	$-C_6H_5SO2NH2$	H
$-CH_2SOC_2H_5$	$-C_6H_5SO2NH2$	H
$-CH2SOC6H5$	$-C_6H_5SO2NH2$	H
$-CH_2SO_2CH_3$	$-C_6H_5SO2NH2$	H
$-CH_2SO_2C_2H_5$	$-C_6H_5SO2NH2$	H
$-CH_2SO_2C_6H_5$	$-C_6H_5SO2NH2$	H
$-CF_3$	$-C_6H_5SO2NH2$	7-F
$-CF_3$	$-C_6H_5SO2NH2$	8-F
$-CF_3$	$-C_6H_5SO2NH2$	9-F
$-CF_3$	$-C_6H_5SO2NH2$	8-Cl

TABLE XV (cont.)

General Structure Io

R^1	R^2	R^4
$-CF_3$	$-C_6H_5SO_2NH_2$	9-Cl
$-CF_3$	$-C_6H_5SO_2NH_2$	7,8-(OCH_2O)-
$-CF_3$	$-C_6H_5SO_2NH_2$	8-$N(CH_3)_2$
$-CF_3$	$-C_6H_5SO_2NH_2$	8-OCH_3
$-CF_3$	$-C_6H_5SO_2NH_2$	7-F, 8-OCH_3
$-CF_3$	$-C_6H_5SO_2NH_2$	7-Cl, 8-OCH_3
$-CF_3$	$-C_6H_5SO_2NH_2$	8-Cl, 7-F
$-CF_3$	$-C_6H_5SO_2NH_2$	8-CH_3
$-CF_3$	$-C_6H_5SO_2NH_2$	7-F, 8-CH_3
$-CF_3$	$-C_6H_5SO_2NH_2$	7,8-F
$-CF_3$	$-C_6H_5SO_2NH_2$	8-SCH_3
$-CF_3$	$-C_6H_5SO_2NH_2$	7-F, 8-SCH_3
$-CF_3$	$-C_6H_5SO_2NH_2$	8-$SOCH_3$
$-CF_3$	$-C_6H_5SO_2NH_2$	7-F, 8-$SOCH_3$
$-CF_3$	$-C_6H_5SO_2NH_2$	7-F, 8-CH_3
$-CF_3$	thienylSO_2NH_2	7-F, 8-OCH_3
$-CF_3$	$-C_6H_5F$	8-SO_2NH_2
$-CF_3$	$-C_6H_5Cl$	8-SO_2NH_2
$-CF_3$	$-C_6H_5OCH_3$	8-SO_2NH_2
$-CF_3$	$-C_6H_5CH_3$	8-SO_2NH_2
$-CF_3$	$-C_6H_5SOCH_3$	8-SO_2NH_2

TABLE XVI

General Structure Ip

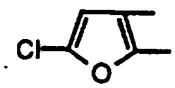
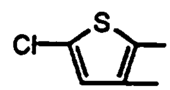
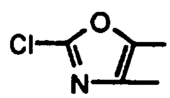
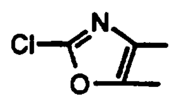
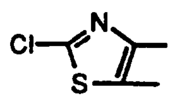
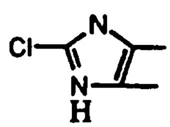
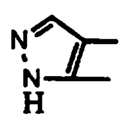
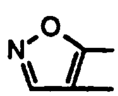
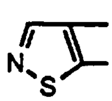
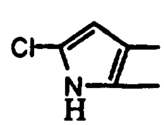
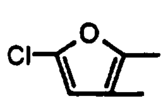
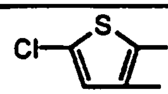
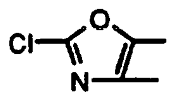
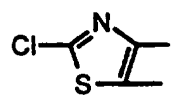
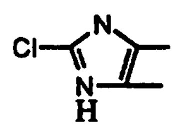
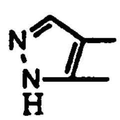
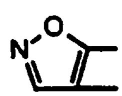
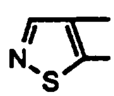
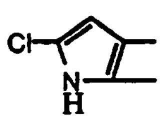
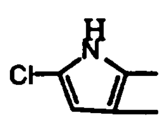
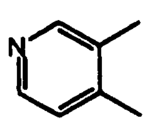
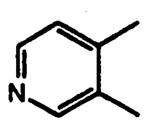
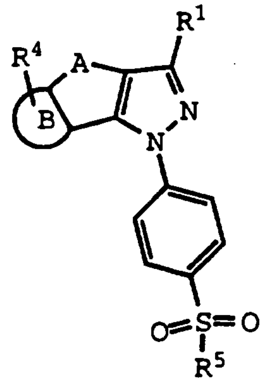
B	R^2
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2CH_3$
	$-C_6H_5SO_2NH_2$

TABLE XVI (cont.)

B	R^2
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$
	$-C_6H_5SO_2NH_2$

Within Formula I there is a subclass of compounds of high interest represented by Formula II:



(II)

wherein A is $-(CH_2)_m-O-(CH_2)_n-$ or $-(CH_2)_m-S(O)_p-(CH_2)_n-$; wherein m is 0 or 1; wherein n is 0 or 1; wherein p is 0 or 1; wherein B is selected from aryl and heteroaryl; wherein R^1 is selected from haloalkyl, hydroxyalkyl, aminocarbonyl, alkoxycarbonyl and cyano; wherein R^4 is one or more radicals selected from hydrido, halo, alkyl and alkoxy; and wherein R^5 is selected from alkyl and amino; or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds consists of those compounds of Formula II wherein A is $-(CH_2)_m-O-(CH_2)_n-$ or $-(CH_2)_m-S(O)_p-(CH_2)_n-$; wherein m is 0 or 1; wherein n is 0 or 1; wherein p is 0 or 1; wherein B is selected from phenyl and five membered heteroaryl; wherein R^1 is selected from lower haloalkyl, lower hydroxyalkyl, aminocarbonyl, lower alkoxycarbonyl and cyano; wherein R^4 is one or more radicals selected from hydrido, halo, lower alkyl and lower alkoxy; and wherein R^5 is selected from lower alkyl and amino; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula II wherein A is $-(CH_2)_m-O-(CH_2)_n-$ or $-(CH_2)_m-S(O)_p-(CH_2)_n-$; wherein m is 0 or 1; wherein n is 0 or 1; wherein p is 0 or 1;

wherein B is selected from phenyl, thienyl, furyl and pyrrolyl; wherein R^1 is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxymethyl, hydroxyethyl, aminocarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and cyano; wherein R^4 is one or more radicals selected from hydrido, fluoro, chloro, bromo, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, hexyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy and *tert*-butoxy; and wherein R^5 is selected from methyl and amino; or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula II consists of compounds and pharmaceutically-acceptable salts thereof as follows:

4-[3-(difluoromethyl)-1,5-dihydro-7-methyl-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

7-fluoro-1,5-dihydro-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazole;

4-[1,5-dihydro-7,8,9-trimethoxy-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[6,8-difluoro-1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[3-cyano-7-fluoro-1,5-dihydro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-7-fluoro-1,5-dihydro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-7-methyl-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[3-cyano-7-fluoro-1,5-dihydro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]-N-[(dimethylamino)methylene]benzenesulfonamide;

4-[3-(difluoromethyl)-1,5-dihydro-7-methyl-[2]benzenethiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-fluoro-1,5-dihydro-3-(hydroxymethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-3-(trifluoromethyl)-[1,3]dioxolo[6,7][2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-chloro-3-(difluoromethyl)-1,5-dihydro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-chloro-1,5-dihydro-3-trifluoromethyl-thieno[3',2':4,5]thiopyrano-s-oxide[3,2-c]pyrazol-1-yl]benzenesulfonamide;

methyl [1-(4-aminosulfonylphenyl)-1,5-dihydro-7-fluoro-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-3-yl]carboxylate;

[1-(4-aminosulfonylphenyl)-1,5-dihydro-7-fluoro-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-3-yl]carboxamide;

4-[1,5-dihydro-6-fluoro-7-methoxy-3-(difluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-7-fluoro-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

1,5-dihydro-6-fluoro-7-methoxy-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazole;

4-[1,4-dihydro-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

methyl [1-[4-(aminosulfonyl)phenyl]-1,4-dihydro-[1]benzopyrano[4,3-c]pyrazol-3-yl]carboxylate;

4-[1,4-dihydro-6-fluoro-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[3-(trifluoromethyl)-1H-benzofuro[3,2-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

methyl [1-[4-(aminosulfonyl)phenyl]-1,4-dihydro-[1]benzothiopyrano[4,3-c]pyrazol-3-carboxylate;

4-[6,7-dichloro-1,4-dihydro-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-7-fluoro-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-6-isopropyl-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-7,8-dimethoxy-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-7-methoxy-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-7-methyl-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-chloro-1,4-dihydro-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-7-methyl-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

1,5-dihydro-1-[4-(methylsulfonyl)phenyl]-7-methyl-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazole;

4-[7-chloro-1,5-dihydro-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-chloro-1,5-dihydro-3-trifluoromethyl-[2]thienothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide; and

4-[3-cyano-1,4-dihydro[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical. Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about

ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, iso-amyl, hexyl and the like. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy

radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. More preferred alkoxyalkyl radicals are "lower alkoxyalkyl" radicals having one to six carbon atoms and one or two alkoxy radicals. Examples of such radicals include methoxymethyl, methoxyethyl, ethoxyethyl, methoxybutyl and methoxypropyl. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" or haloalkoxyalkyl radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. The term "heterocyclic" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Such heterocyclic radicals preferrably include ring systems having 3 to 10 members. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo[1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] and isothiazolyl; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuryl, benzothienyl, and the like. Said "heterocyclic" radicals may have 1 to 3 substituents such as lower alkyl, hydroxy, oxo, amino and lower

alkylamino. More preferred heteroaryl radicals include fiv to six membered heteroaryl radicals. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The term "alkylthioalkyl" embraces alkylthio radicals attached to an alkyl radical. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms and an alkylthio radical as described above. Examples of such radicals include methylthiomethyl. The term "arylthio" embraces radicals containing an aryl radical, attached to a divalent sulfur atom, such as a phenylthio radical. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl. The term "alkylsulfinylalkyl" embraces alkylsulfinyl radicals attached to an alkyl radical, where alkyl and alkylsulfinyl are defined as above. More preferred alkylsulfinylalkyl radicals are "lower alkylsulfinylalkyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfinylalkyl radicals include methylsulfinylmethyl. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon

atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The term "alkylsulfonylalkyl" embraces alkylsulfonyl radicals attached to an alkyl radical, where alkyl and alkylsulfonyl are defined as above. More preferred alkylsulfonylalkyl radicals are "lower alkylsulfonylalkyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonylalkyl radicals include methylsulfonylmethyl, ethylsulfonylmethyl and propylsulfonylmethyl. The term "arylsulfonyl" embraces aryl radicals as defined above, attached to a sulfonyl radical. Examples of such radicals include phenylsulfonyl. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denotes NH_2O_2S-. The terms "N-alkylaminosulfonyl" and "N,N-dialkylaminosulfonyl" denote aminosulfonyl radicals substituted, respectively, with one alkyl radical, a cycloalkyl ring, or two alkyl radicals. The terms "N-arylaminosulfonyl" and "N-alkyl-N-arylaminosulfonyl" denote aminosulfonyl radicals substituted with one aryl radical or one alkyl and one aryl radical, respectively. The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include formyl, alkanoyl and aroyl radicals. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$. The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes -(C=O)-. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Preferably, "lower alkoxycarbonyl" embraces alkoxy radicals having one to six carbon atoms. Examples of such "lower alkoxycarbonyl" ester radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The term "alkylcarbonyl" includes radicals having

alkyl, aryl and aralkyl radicals, respectively, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred alkylcarbonyl radicals are "lower alkylcarbonyl" radicals having one to six carbon atoms. Examples of such radicals include methylcarbonyl and ethylcarbonyl. The term "alkylcarbonylalkyl" embraces radicals having "alkylcarbonyl", as defined above substituted to an alkyl radical. More preferred alkylcarbonylalkyl radicals are "lower alkylcarbonylalkyl" having lower alkylcarbonyl radicals as defined above attached to one to six carbon atoms. Examples of such lower alkylcarbonylalkyl radicals include methylcarbonylmethyl. The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. More preferred alkoxycarbonylalkyl radicals are "lower alkoxycarbonylalkyl" having lower alkoxycarbonyl radicals as defined above attached to one to six carbon atoms. Examples of such lower alkoxycarbonylalkyl radicals include methoxycarbonylmethyl. The term "carboxyalkyl" embraces radicals having a carboxy radical as defined above, attached to an alkyl radical. More preferred are "lower carboxyalkyl" having alkyl portions of one to six carbon atoms. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" having one to six carbon atoms. Examples include aminomethyl, aminoethyl and aminobutyl. The term "alkylamino" denotes amino groups which have been substituted with one or two alkyl radicals. Preferred alkylamino radicals are "lower alkylamino" having alkyl portions of one to six carbon atoms. Examples include N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like. The term "alkylaminocarbonyl" embraces alkylamino radicals, as described above, attached to a carbonyl radical. More preferred alkylaminocarbonyl radicals are "lower

alkylaminocarbonyl" having lower alkylamino radicals, as described above, attached to a carbonyl radical. Examples of such radicals include N-methylaminocarbonyl and N,N-dimethylcarbonyl. The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "arylaminocarbonyl" embraces arylamino radicals, as described above, connected to a carbonyl radical. An example of such radicals includes phenylaminocarbonyl. The term "N-alkyl-N-arylaminocarbonyl" embraces arylamino radicals, as described above, to a carbonyl radical. An example of such radicals includes phenylaminocarbonyl. The term "aminocarbonyl" denotes an amide group of the formula $-C(=O)NH_2$. The term "N-alkyl-N-arylaminocarbonyl" embraces aminocarbonyl radicals, as described above, substituted with one alkyl and one aryl radical. An example of such radicals is N-methyl-N-phenylaminocarbonyl. The term "aminocarbonylalkyl" denotes an aminocarbonyl radical attached to an alkyl radical, as described above. An example of such radicals is aminocarbonylmethyl. The term "amidino" denotes an $-C(=NH)-NH_2$ radical. The term "cyanoamidino" denotes an $-C(=N-CN)-NH_2$ radical. The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "acylamino" embraces an amino radical substituted with an acyl group. An examples of an "acylamino" radical is acetylamino ($CH_3C(=O)-NH-$).

The present invention comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of Formula I in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of treating inflammation or inflammation-associated disorders in a subject, the method comprising administering to the subject having such inflammation or disorder a therapeutically-effective amount of a compound of Formula I.

Compounds of Formula I would also be capable of inhibiting cytokines, such as TNF, IL-1, IL-6, and IL-8. As such, the compounds can be used in the manufacture of a medicament or in a method for the treatment for the prophylactic or therapeutic treatment of diseases mediated by cytokines, such as TNF, IL-1, IL-6, and IL-8.

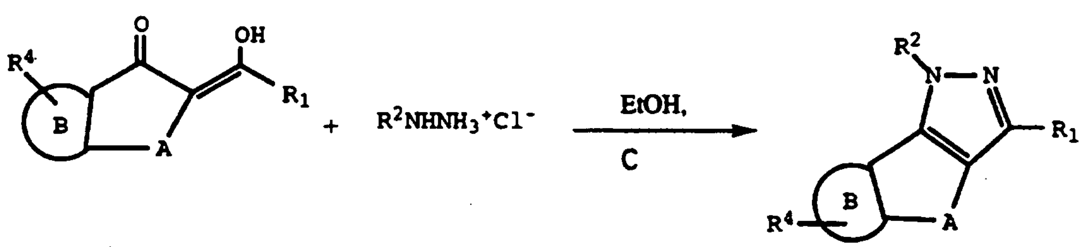
Also included in the family of compounds of Formula I are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, *p*-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethylsulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, salicylic, galactaric and

galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, choline, chloroprocaine, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I.

GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized according to the following procedures of Schemes I-XII, wherein the R^1-R^5 substituents are as defined for Formulas I-II, above, except where further noted.

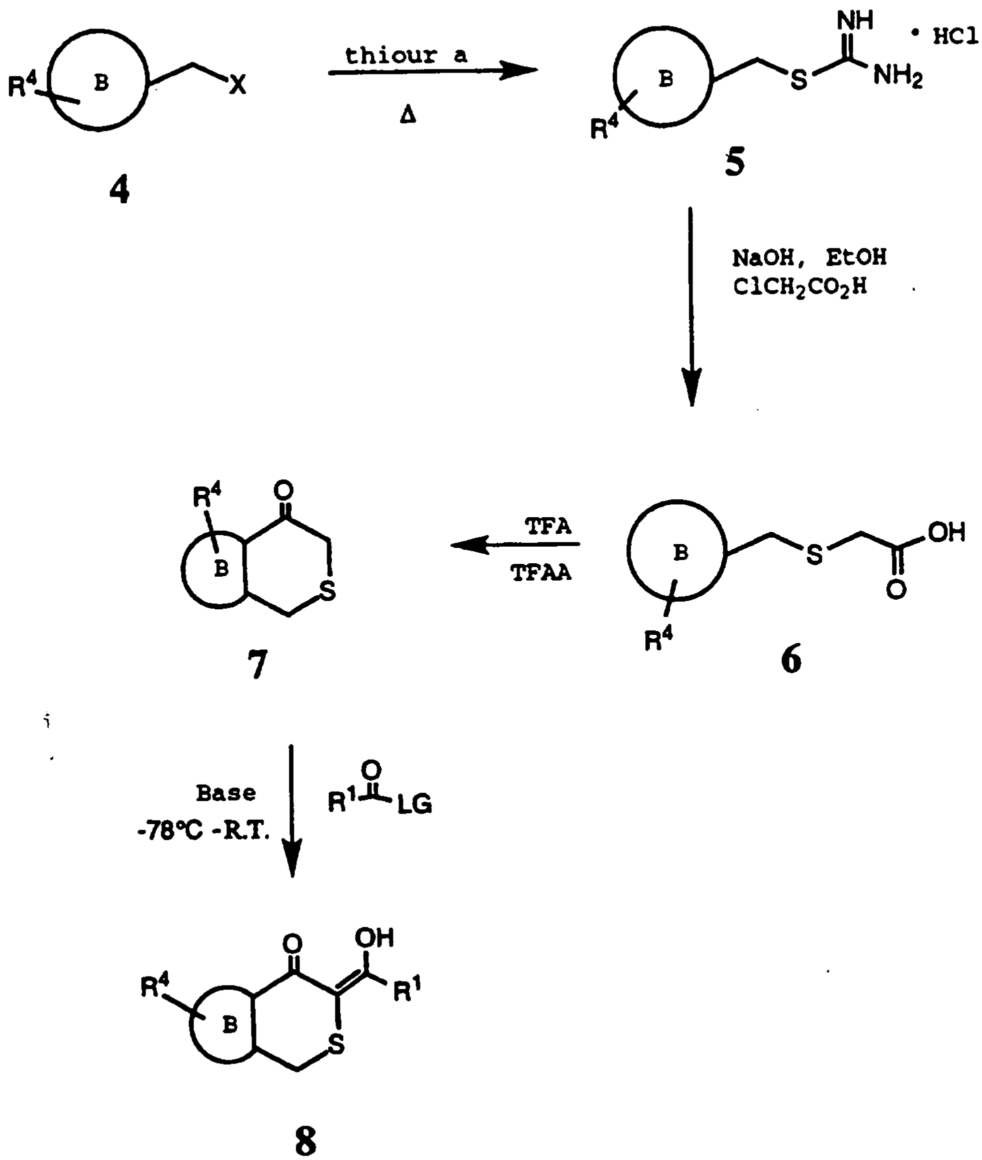
SCHEME I



1 2 3

Synthetic Scheme I illustrates the procedure used to prepare the antiinflammatory pyrazoles 3 of the present invention. 1,3-Dicarbonyl compounds such as **1**, or the shown enol form which is in equilibrium to the diketone, are reacted with a hydrazine hydrochloride **2** in warm ethanol to provide the pyrazoles 3 via a condensation reaction.

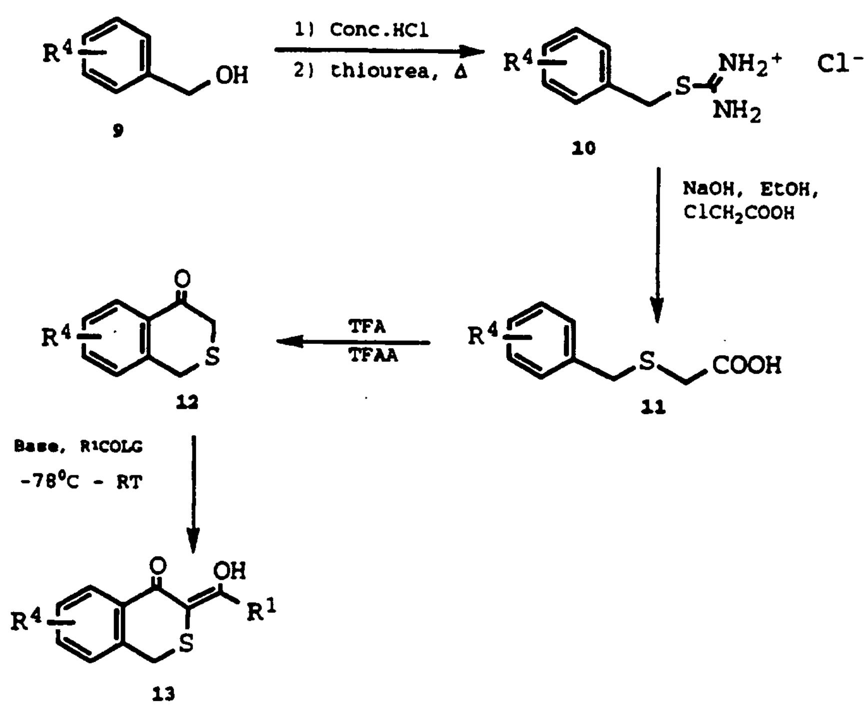
SCHEME II



Synthetic Scheme II illustrates the four step procedure for the preparation of substituted diketones **8**. In step one, an appropriately substituted methyl halide **4** (where X is chloro for example) is converted into the corresponding thiouronium salt **5** upon treatment with thiourea. In step two, the thiouronium salt **5** is converted according to the procedure of Lumma and Berchtold (*J. Org. Chem.*, **34**, 1566 (1969)) to the free mercaptide and then trapped with chloroacetic acid or a related salt to provide the acetic acid

derivatives **6**. In step three, the acids **6** are reacted with trifluoroacetic anhydride (TFAA) in trifluoroacetic acid (TFA) to give the ketones **7**. In step four, the ketones **7** are first treated with base, such as sodium methoxide or lithium diisopropylamide (LDA), followed by condensation with a suitable acylating agent, R^1COLG, (where LG represents an appropriate leaving group such as methoxy, chloro, imidazole and the like) in an appropriate solvent, such as methanol, diethyl ether or tetrahydrofuran, to provide the desired diketones **8** which are suitable for conversion into antiinflammatory pyrazoles as illustrated in Scheme I.

SCHEME III

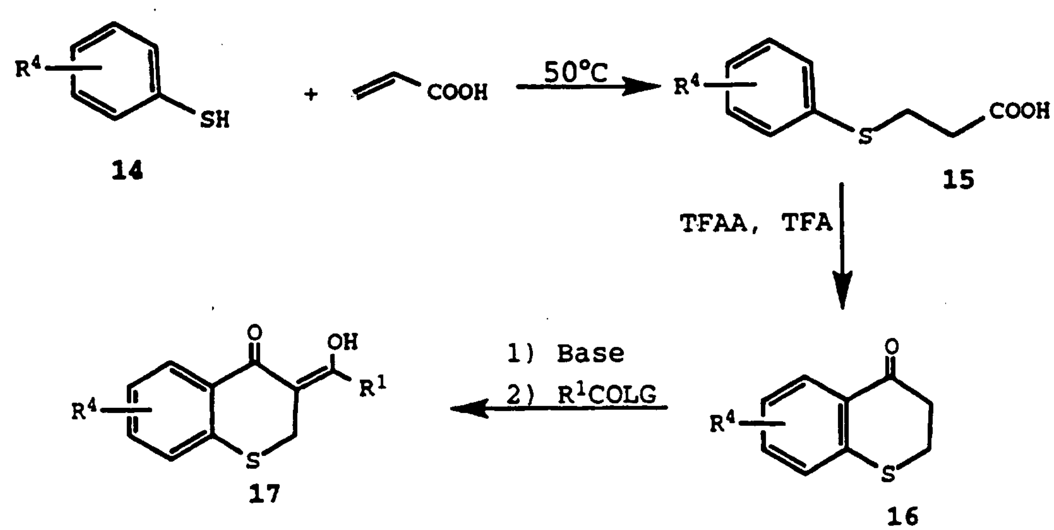


Synthetic Scheme III illustrates the four step procedure for the preparation of substituted isothiochromanone 1,3-carbonyl derivatives **13**. In step one, an appropriately substituted benzyl alcohol **9** is converted into the corresponding benzyl chloride by stirring with concentrated hydrochloric acid and then

immediately converted into a thiouronium salt **10** upon treatment with thiourea at reflux. In step two, the thiouronium salt is converted to the free mercaptide and then trapped with chloroacetic acid or a related salt to provide the acetic acid derivatives **11**. In step three, the acids **11** are reacted with trifluoroacetic anhydride (TFAA) in trifluoroacetic acid (TFA) to give the isothiochromanone products **12**. In step four, the isothiochromanones **12** are first treated with base, such as sodium methoxide, sodium bistrimethylsilylamide or lithium diisopropylamide (LDA), followed by condensation with a suitable acylating agent, R^1COLG, (where LG is defined as in Scheme II) in an appropriate solvent, such as methanol, diethyl ether or tetrahydrofuran, to provide 1,3-dicarbonyl compounds **13** which are suitable for conversion into antiinflammatory pyrazoles as illustrated in Scheme I.

Alternatively, the dicarbonyl compounds **13** can be directly prepared from commercially available isothiochromanones **12**. The thiouronium salts **10** can be prepared from commercially available benzyl halides.

SCHEME IV

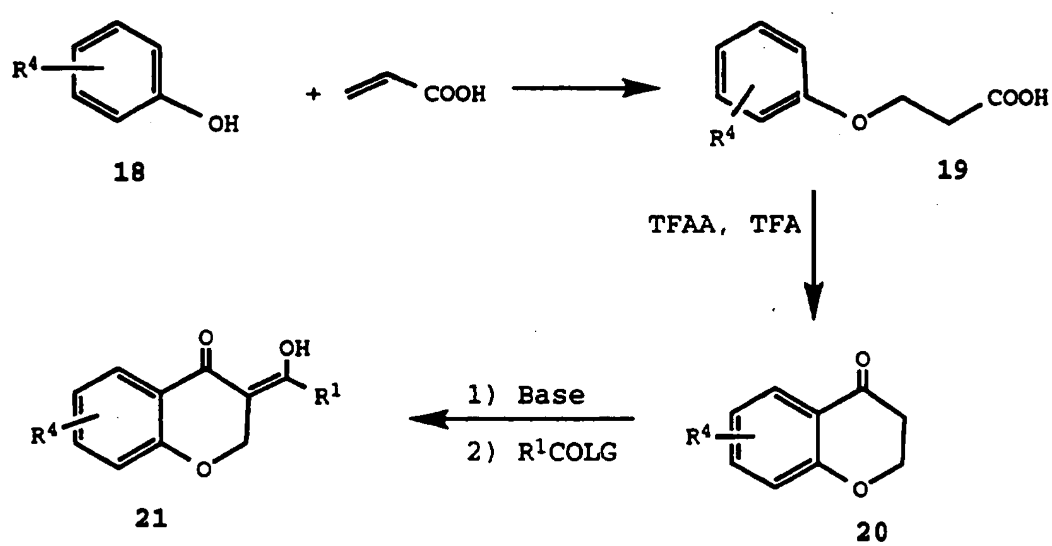


Synthetic Scheme IV illustrates a three step

procedure used for the preparation of substituted thiochromanone 1,3-dicarbonyl derivatives **17**. In step one, an appropriate substituted thiophenol **14** is converted into the corresponding propionic acid derivatives **15** upon treatment with acrylic acid at a temperature in a range of room temperature to about 50°C. In step two, the propionic acids **15** are subjected to treatment with a mixture of trifluoroacetic anhydride and trifluoroacetic acid to effect intramolecular Friedel-Crafts acylation, thus providing thiochromanones **16**. In the last step, substituted thiochromanones **16** are first treated with a base, such as lithium diisopropyl amide or sodium methoxide (LDA), followed by condensation with suitable acylating agents R^1COLG (as defined in Scheme II) in an appropriate solvent such as diethylether, methanol or tetrahydrofuran to provide the 1,3-dicarbonyl compounds **17** which are suitable for conversion into antiinflammatory pyrazoles as illustrated in Scheme I.

Alternatively, the dicarbonyl compounds **17** can be directly prepared from commercially available thio-4-chromanones **16**.

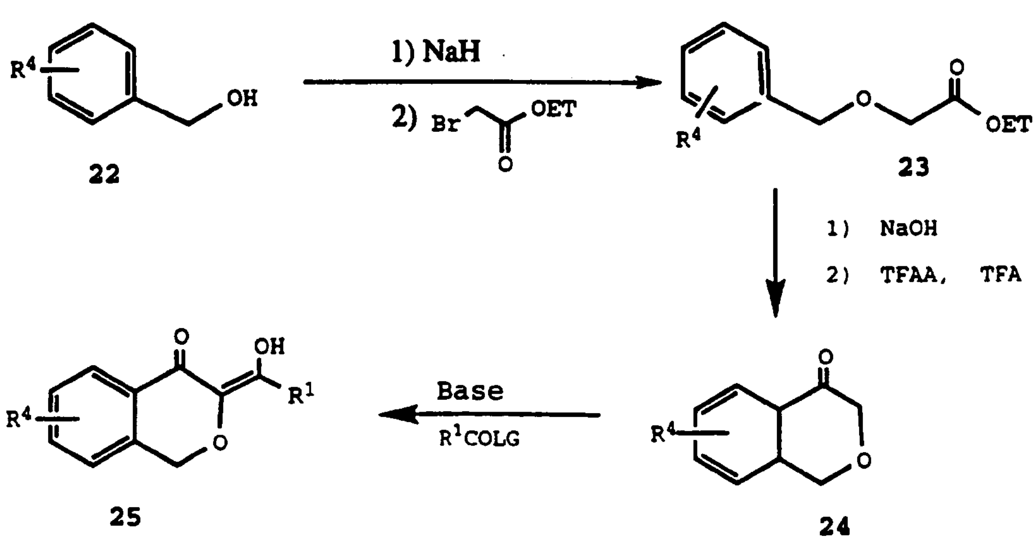
SCHEME V



Synthetic Scheme V details the three step procedure used to prepare substituted 1,3-dicarbonyl chromanone derivatives **21**. In step one, substituted phenols **18** are condensed with acrylic acid to afford 3-phenoxypropionic acids **19**. In step two, the acids **19** are treated with a mixture of trifluoroacetic anhydride and trifluoroacetic acid to affect intramolecular Friedel-Crafts acylation affording selected chromanones **20**. In step three, substituted chromanones **20** are first treated with base, such as lithium diisopropylamide (LDA) or sodium methoxide followed by condensation with suitable acylating agents, R^1COLG (where LG represents leaving group as previously defined in Scheme II in an appropriate solvent such as diethyl ether or methanol) to provide 1,3-dicarbonyl compounds **21** which are suitable for conversion into antiinflammatory pyrazoles as illustrated in Scheme I.

Alternatively, the dicarbonyl compounds **21** can be directly formed from commercially available chromanones **20**.

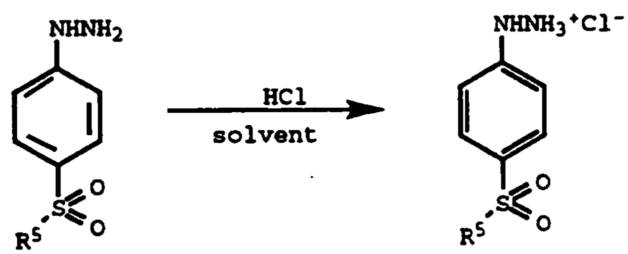
SCHEME VI



Synthetic Scheme VI illustrates a three step procedure used to prepare substituted 1,3-dicarbonyl

isochromanone derivatives **25**. In step one, selected benzyl alcohol derivatives **22** are treated with sodium hydride and subsequently treated with ethyl bromoacetate to provide the desired ethers **23**. In step two, the ester group of **23** is hydrolyzed with aqueous sodium hydroxide and then treated with a mixture of trifluoroacetic acid and trifluoroacetic anhydride to promote intramolecular Friedel-Crafts acylation affording isochromanone **24** derivatives. In the third step, the isochromanones **24** are first treated with a base such as lithium diisopropylamide (LDA) or sodium methoxide followed by condensation with suitable acylating agents (R^1COLG) to provide the 1,3-dicarbonyl compounds **25** which were suitable for conversion into antiinflammatory pyrazoles as illustrated in Scheme I.

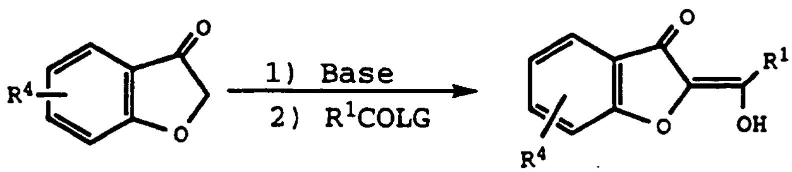
SCHEME VII



26 **27**

Synthetic Scheme VII illustrates a procedure used to prepare the methylsulfonylphenylhydrazine hydrochloride and the sulfonamidylphenylhydrazine hydrochlorides **27** as used in Scheme I. The sulfonylphenylhydrazine **26** is converted to the hydrochloride salt by stirring with a 4N solution of hydrochloric acid in a solvent such as dioxane.

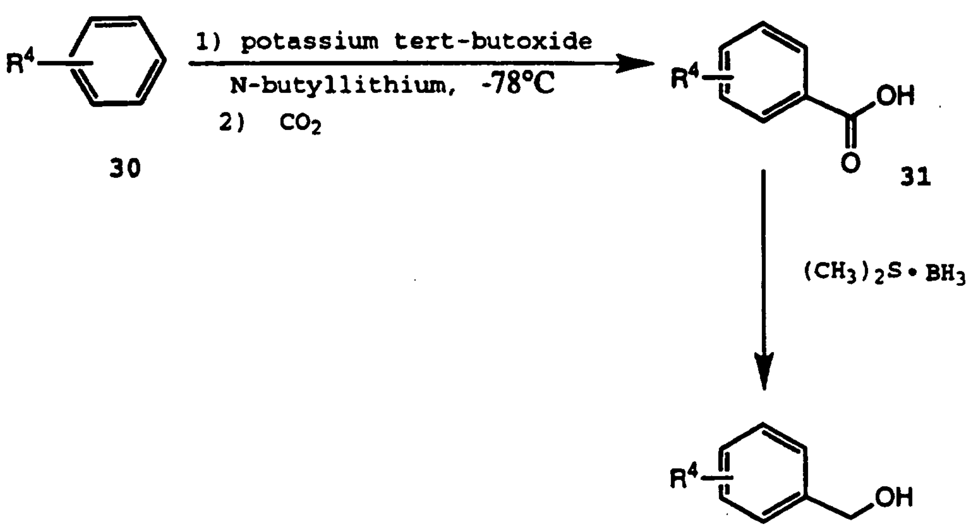
SCHEME VIII



28 29

Synthetic Scheme VIII illustrates a procedure used to prepare substituted 3-coumaranones **29**. Coumaranones **28** are first treated with a base, such as lithium diisopropyl amide or sodium methoxide (LDA) followed by condensation with suitable acylating agents R^1COLG (as defined in Scheme II) in an appropriate solvent such as diethylether, methanol or tetrahydrofuran to provide the 1,3-dicarbonyl compounds **29** which are suitable for conversion into antiinflammatory pyrazoles as illustrated in Scheme I.

SCHEME IX

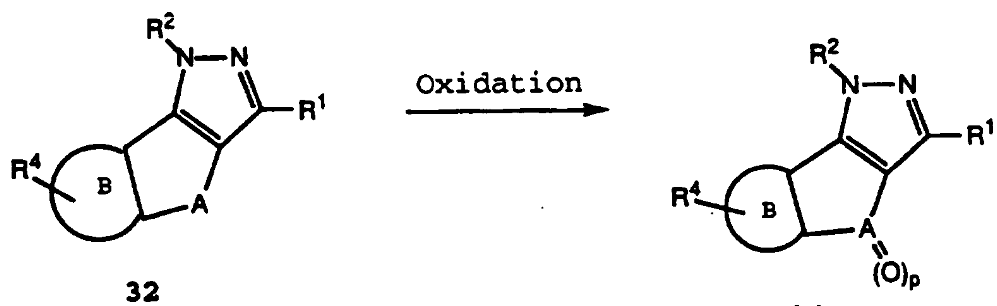


9

Synthetic Scheme IX illustrates a two step procedure used for the preparation of substituted benzylalcohols **9**. In step one, a mixture of potassium

tert-butoxide and anhydrous tetrahydrofuran, cooled to -78°C and treated with a 1.6 M solution of n-butyllithium in hexanes, is added to an appropriate substituted benzene **30** the anion thereby generated is reacted with carbon dioxide to yield the benzoic acid **31**. In step two, the benzoic acid **31** is dissolved in a solvent, such as tetrahydrofuran, and treated with a reducing agent, such as borane dimethyl sulfide complex, to form the desired benzyl alcohol **9**.

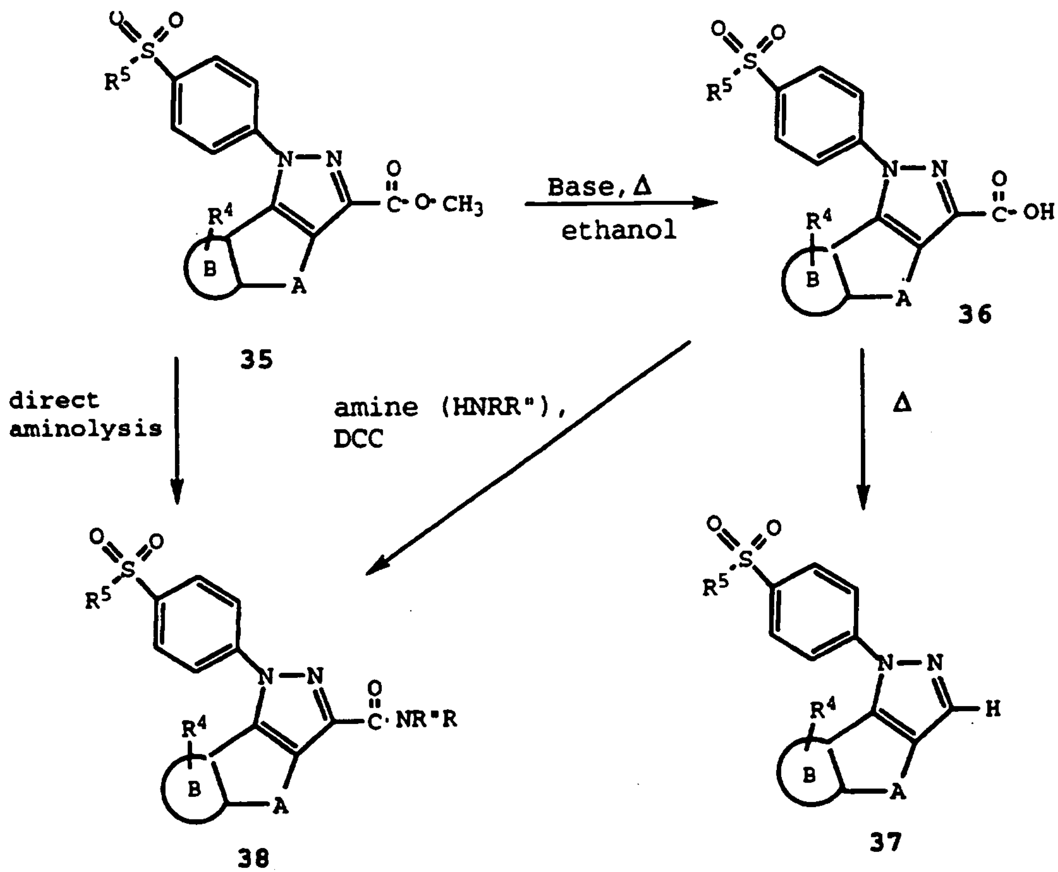
SCHEME X



32 **34**

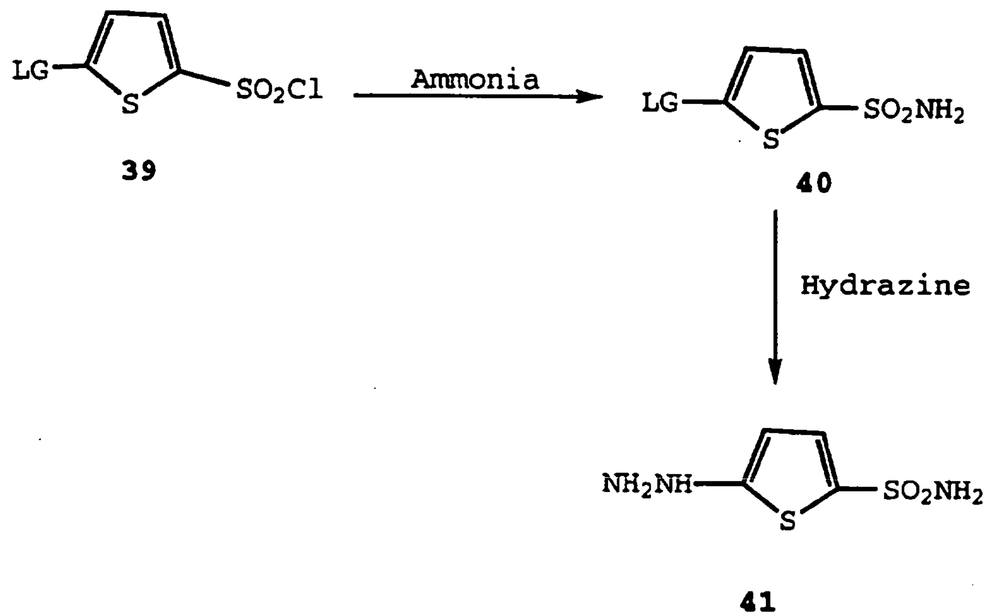
Synthetic Scheme X illustrates a procedure used for the preparation of the antiinflammatory oxidized thio-containing fused tricyclic pyrazoles **33**. The appropriate pyrazole **32** from Scheme I, where A is S or $-(CH_2)_mS(CH_2)_n-$, is treated with an oxidizing agent such as *m*-chloroperbenzoic acid (MCPBA) or hydrogen peroxide. Compounds having differing amounts of oxidation (sulfinyls and sulfones) can be separated, such as by chromatography.

SCHEME XI



Synthetic Scheme XI shows procedures for preparing antiinflammatory agents **36**, **37** and **38** of Formula I. The esters **35**, which can be prepared as shown in Scheme I, is dissolved in aqueous ethanol and a base such as 10% NaOH is added. The reaction is heated to reflux to give the acids **36**. The acids **36** can be converted to the fused pyrazole with a hydrido radical by decarboxylation by heating to about 290°C to give the decarboxylated products **37**. The acids **36** also can be converted to the appropriate amides **38** by dissolving in methanol and treating with an appropriate amine in the presence of a condensing agent such as dicyclohexylcarbodiimide (DCC). The amides **38** can also be prepared by direct aminolysis of **35**.

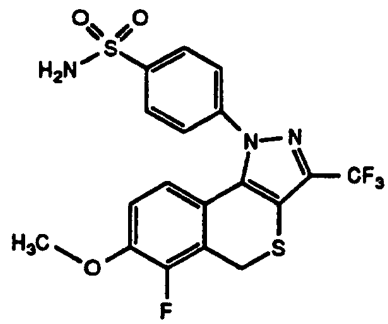
SCHEME XII



Synthetic Scheme XII shows the two step procedure for preparation of substituted heteroarylhydrazine compounds **41** as used in Scheme I where R^2 is thienyl. In step 1, the heteroarylsulfonyl chloride **39** (where LG represents a leaving group such as halo) is treated with ammonia to give the heteroaryl sulfonamides **40**. In step 2, the heteroaryl sulfonamides **40** are treated with hydrazine to give the substituted heteroarylhydrazines **41**.

The following examples contain detailed descriptions of the methods of preparation of compounds of Formula I-II. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated.

EXAMPLE 1



4-[1,5-Dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 2-fluoro-3-methoxybenzoic acid.

A mixture of potassium *tert*-butoxide (30.80 g, 274 mmol) and anhydrous tetrahydrofuran (300 mL) was cooled to -78°C and treated with a 1.6 M solution of n-butyllithium (172 mL, 275 mmol) in hexanes. After stirring for 15 minutes, 2-fluoroanisole (31.35 g, 248 mmol) was added and the reaction was stirred an additional 1.8 hours. The reaction was poured into dry ice and warmed to room temperature. Water (250 mL) was added and after extracting with ether (160 mL), the aqueous layer was acidified with concentrated hydrochloric acid, and filtered to give 2-fluoro-3-methoxybenzoic acid (21.43 g, 51%) as a yellow solid: mp 155-160°C; ^{1}H NMR (acetone-d_6) 300 MHz 7.46 (ddd, J=6.0 Hz J=1.8 Hz J=1.4 Hz, 1H) 7.36 (dt, J=1.6 Hz J=8.1 Hz, 1H) 7.20 (dt, J=1.4 Hz J=8.1 Hz, 1H) 3.92 (s, 3H); ^{19}F NMR (acetone-d_6) 300 MHz -134.04 (m). Mass spectrum: M+H=171.

Step 2. Preparation of 2-fluoro-3-methoxybenzyl alcohol.

2-Fluoro-3-methoxybenzoic acid from Step 1 (16.65 g, 98 mmol) was dissolved in anhydrous

tetrahydrofuran (60 mL), cooled in an ice bath, and treated with borane dimethyl sulfide complex (19 mL, 190 mmol). The reaction was stirred at room temperature for 4.2 hours, quenched by the slow addition of methanol, and concentrated *in vacuo*. The residue was dissolved in ethyl acetate, treated with 3N hydrochloric acid and filtered through diatomaceous earth. The organic layer of the filtrate was collected, washed with $NaHCO_3$, brine, dried over $MgSO_4$ and reconcentrated *in vacuo* to give 2-fluoro-3-methoxybenzyl alcohol (12.35 g, 81%) as a white solid: mp 53-57°C; ^1H NMR (acetone-d_6) 300 MHz 7.07 (m, 3H) 4.67 (d, J=5.8 Hz, 2H) 4.24 (t, J=5.8 Hz, 1H) 3.86 (s, 3H); ^{19}F NMR (acetone-d_6) 300 MHz -144.77(m).

<u>Step 3. Preparation of 2-fluoro-3-methoxybenzyl chloride.</u>

2-Fluoro-3-methoxybenzyl alcohol from Step 2 (12.16 g, 78 mmol) was dissolved in concentrated hydrochloric acid (60 mL) and hydrochloric acid gas was bubbled through the solution for 3 minutes. The reaction was stirred at room temperature (21 hours). The reaction mixture was extracted with ether, dried over $MgSO_4$ and concentrated *in vacuo* to give 2-fluoro-3-methoxybenzyl chloride (10.36 g, 76%) as a green oil: ^1H NMR (acetone-d_6) 300 MHz 7.12 (m, 2H) 7.05 (m, 1H) 4.73 (s, 2H) 3.89 (s, 3H); ^{19}F NMR (acetone-d_6) 300 MHz -142.07(m).

<u>Step 4. Preparation of S-(2-fluoro-3-methoxybenzyl)-isothiouronium chloride.</u>

Thiourea (4.47 g, 59 mmol) was added to a solution of 2-fluoro-3-methoxybenzyl chloride from Step 3 (10.20 g, 58 mmol) in methanol (25 mL). The reaction was heated to reflux for 3.3 hours, concentrated *in vacuo*, triturated with ether, and filtered to give a white solid (14.65 g, 100%).

Step 5. Preparation of 3-(2-fluoro-3-methoxyphenylthio)propanoic acid.

The thiouronium salt from Step 4 (14.65 g, 58 mmol) was added to sodium chloroacetate (10.44 g, 90 mmol), ethanol (60 mL) and water (25 mL). After heating to reflux, a solution of NaOH (10.66 g, 266 mmol) in water (35 mL) was added to the reaction dropwise. After stirring for 16.6 hours, the reaction was acidified with concentrated hydrochloric acid, extracted with ether, washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and recrystallized from ether/hexane to give a brown solid (7.70 g, 57%): mp 72-74°C; ^1H NMR ($CDCl_3$) 300 MHz 7.03 (m, 1H) 6.91 (m, 2H) 3.89 (d, J=1.0 Hz, 2H) 3.88 (s, 3H) 3.19 (s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz -140.76(m).

Step 6. Preparation of 8-fluoro-7-methoxyisothiochroman-4-one.

The acid from Step 5 (7.63 g, 33 mmol) was dissolved in trifluoroacetic acid (12 mL), treated with trifluoroacetic anhydride (4 mL) and stirred at room temperature (8 minutes). The reaction was poured into 10% Na_2CO_3 (50 mL) and extracted with ethyl acetate, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 8-fluoro-7-methoxyisothiochroman-4-one (5.42 g, 77%) as a brown solid: mp 85-92°C; ^1H NMR ($CDCl_3$) 300 MHz 7.83 (d, J=8.9 Hz, 1H) 7.19 (t, J=8.5 Hz, 1H) 4.01 (s, 2H) 3.98 (s, 3H) 3.55 (s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz -141.24(m).

Step 7. Preparation of 6-fluoro-7-methoxy-3-(trifluoroacetyl)isothiochroman-4-one.

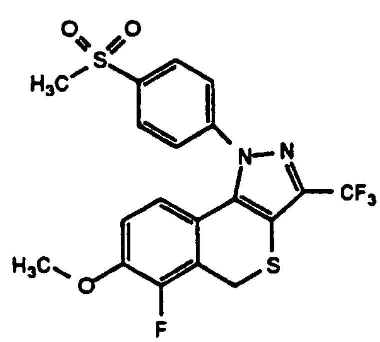
8-Fluoro-7-methoxyisothiochroman-4-one from Step 6 (1.70 g, 8.0 mmol) was dissolved in anhydrous tetrahydrofuran (30 mL), cooled to -78°C, and treated with a 1.0M tetrahydrofuran solution of sodium bistrimethylsilyl amide (10 mL, 10mmol). After 30

minutes, N-trifluoroacetylimidazole (1.85 g in 10.0 mL THF, 11.3 mmol) was added and the reaction was stirred and warmed to room temperature overnight (19.4 hours). The reaction was treated with 1N hydrochloric acid (30 mL). The organic layer was collected, washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and recrystallized from dichloromethane/isooctane to give the diketone (1.14 g, 46%) as a brown solid: mp 162-164°C; ^1H NMR ($CDCl_3$) 300 MHz 15.50 (s, 1H) 7.82 (dd, J=8.9 Hz J=1.0 Hz, 1H) 6.99 (t, J=8.5 Hz, 1H) 3.99 (s, 3H) 3.89 (s, 2H) 2.43 (s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz: -72.46 (s) -140.30 (d). Mass spectrum: M+H=309.

Step 8. Preparation of 4-[6-fluoro-1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

4-Sulfonamidophenylhydrazine hydrochloride (0.77 g, 3.4 mmol) was added to a stirred solution of the diketone from Step 7 (0.93 g, 3.0 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred for 20.4 hours. The reaction mixture was filtered while hot to give the pyrazole as gray needles (0.55 g, 40%): mp 250-252°C; ^1H NMR (acetone-d_6) 300 MHz 8.08 (d, J=8.9 Hz, 2H) 7.85 (d, J=8.7 Hz, 2H) 7.01 (t, J=8.7 Hz, 1H) 6.81 (br s, 2H) 6.72 (dd, J=8.6 Hz J=1.9 Hz, 1H) 4.20 (s, 2H) 3.91 (s, 3H); ^{19}F NMR (acetone-d_6) 300 MHz -63.32 (s) -140.16 (d).

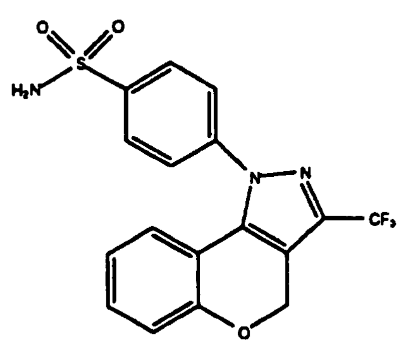
EXAMPLE 2



1,5-Dihydro-6-fluoro-7-methoxy-1-[(4-methylsulfonyl)phenyl]-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazole

4-(Methylsulfonyl)phenylhydrazine (0.75 g, 4.0 mmol) was converted to the hydrochloride salt by stirring with a 4N solution of hydrochloric acid in dioxane (10 mL) for 30 minutes. The dioxane was removed *in vacuo* and the 4-(methylsulfonyl)phenyl hydrazine hydrochloride was combined with the diketone from Example 1, Step 7 (0.89 g, 2.9 mmol) and ethanol (15 mL), heated to reflux and stirred for 14.5 hours. The reaction mixture was filtered while hot and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and with brine, dried over $MgSO_4$, reconcentrated *in vacuo* and passed through a column of silica gel, eluting with 20% ethyl acetate/hexane to give the pyrazole (0.46 g, 35%) as a yellow solid: mp 213-215°C; ^1H NMR (acetone-d_6) 300 MHz 8.15 (d, J=8.7 Hz, 2H) 7.94 (d, J=8.7 Hz, 2H) 7.01 (t, J=8.7 Hz, 1H) 6.73 (d, J=8.7 Hz, 1H) 4.21 (s, 2H) 3.90 (s, 3H) 3.23 (s, 3H); ^{19}F NMR (acetone-d_6) 300 MHz -63.41 (s) -140.17 (d). Mass spectrum: M+=458.1.

EXAMPLE 3



4-[1,4-Dihydro-3-(triflu romethyl)-[1] benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

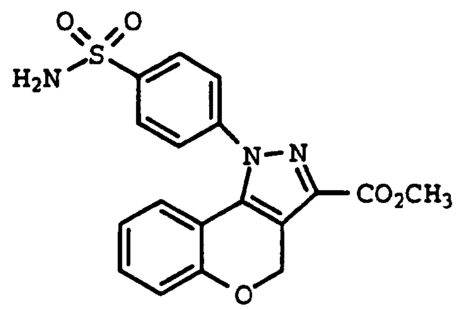
Step 1. Preparation of 3-(trifluoroacetyl)-4-chromanone.

Ethyl trifluoroacetate (9.78 g, 68 mmol) was dissolved in ether (50 mL). To the stirred solution was added 25% sodium methoxide (15.11 g, 70 mmol), followed by 4-chromanone (10.07 g, 68 mmol) dissolved in ether (25 mL). The reaction was stirred at room temperature overnight (18.3 hours), poured into a separatory funnel and washed with 3N hydrochloric acid (20 mL) and with brine (20 mL), dried over $MgSO_4$, concentrated *in vacuo*, and recrystallized from ether/hexane to give a yellow solid (10.72 g, 65%): mp 81-83°C; ^1H NMR ($CDCl_3$) 300 MHz 16.04 (br s, 1H) 7.84 (d, J=7.9 Hz, 1H) 7.51 (m, 1H) 7.09 (m, 1H) 6.98 (d, J=8.5 Hz, 1H) 5.08 (s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz: -72.56 (s). Mass spectrum: M+=244.

Step 2. Preparation of 4-[1,4-dihydro-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

4-Sulfonamidophenylhydrazine hydrochloride (4.57 g, 20.4 mmol) was added to a stirred solution of the diketone from Step 1 (4.59 g, 18.8 mmol) in ethanol (80 mL). The reaction was heated to reflux and stirred overnight (17.3 hours). The reaction mixture was filtered while hot to give the pyrazole as a white solid (3.99 g, 54%). Upon cooling, the filtrate yielded an additional 1.97 g (26%): mp 250-251°C; ^1H NMR (acetone-d_6) 300 MHz 8.14 (d, J=8.7 Hz, 2H), 7.87 (d, J=8.7 Hz, 2H) 7.30 (m, 1H), 7.08 (d, J=8.1Hz, 1H) 6.89 (m, 3H) 5.41 (s, 2H); ^{19}F NMR (acetone-d_6) 300 MHz -62.42 (s). High resolution mass spectrum Calc'd. for $C_{17}H_{12}F_3N_3O_3S$: 395.0551. Found: 395.0551.

EXAMPLE 4



Methyl [1-[4-(aminosulfonyl)phenyl]-1,4-dihydro-[1]benzopyrano[4,3-c]pyrazol-3-yl]carboxylate

<u>Step 1. Preparation of methyl-3-(1-oxo-2-carboxy)-4-chromanone.</u>

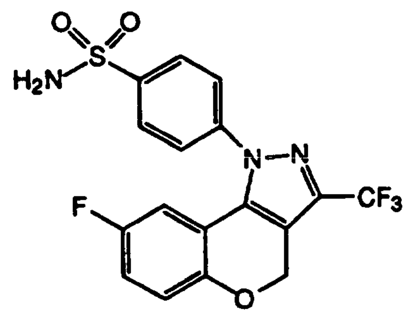
4-Chromanone (9.72 g, 65.6 mmol) was added to dimethyl oxalate (8.92 g, 75.5 mmol) and methanol (75 mL). The solution was treated with sodium methoxide (25%) in methanol (18.52 g, 85.7 mmol) and stirred at room temperature for 18.8 hours. The reaction was treated with 3N hydrochloric acid (30 mL), filtered, and recrystallized from ethyl acetate/isooctane to give the diketone (11.31 g, 74%) as a yellow solid: mp 85-87°C; ^{1}H NMR (acetone-d_6) 300 MHz 7.87 (d, J=7.9 Hz, 1H) 7.61 (m, 1H) 7.14 (m, 1H) 7.02 (d, J=8.3 Hz, 1H) 5.35 (s, 2H) 3.92 (s, 3H). Mass spectrum: M+Li=234.

<u>Step 2. Preparation of methyl [1-[4-(aminosulfonyl)phenyl]-1,4-dihydro-[1]benzopyrano[4,3-c]pyrazol-3-yl]carboxylate.</u>

4-Sulfonamidophenylhydrazine hydrochloride (6.52 g, 29.1 mmol) was added to a stirred solution of the diketone from Step 1 (6.23 g, 26.6 mmol) in methanol (MeOH) (150 mL). The reaction was heated to reflux and stirred for 15.1 hours. The reaction mixture was filtered, washed with MeOH and dried under vacuum to

give the pyrazole as a pale green solid (9.81 g, 96%): mp > 304°C; ^{1}H NMR (DMSO-d_6) 300 MHz 8.02 (d, J=8.7 Hz, 2H) 7.83 (d, J=8.5 Hz, 2H) 7.60 (br s, 2H) 7.25 (2d, 1H) 7.06 (d, J=7.5 Hz,1H) 6.84 (2d, 1H) 6.71 (d, J=7.9 Hz, 1H) 5.46 (s, 2H) 3.85 (s, 3H). Mass spectrum: M+H = 386.

EXAMPLE 5



4-[1,4-Dihydro-8-fluoro-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

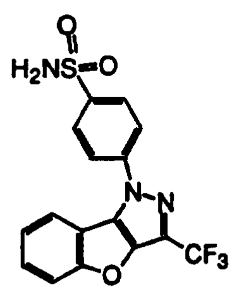
<u>Step 1. Preparation of 6-fluoro-3-(trifluoroacetyl)-4-chromanone</u>.

Ethyl trifluoroacetate (4.33 g, 30 mmol) was dissolved in ether (25 mL) and treated with sodium methoxide (25%, 7.08 g, 33 mmol). To the stirred solution was added 6-fluoro-4-chromanone (4.92 g, 30 mmol) and additional ether (10mL). The reaction was stirred at room temperature overnight (19.0 hours) and treated with 3N hydrochloric acid (15 mL). The organic layer was collected, washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and recrystallized from ether/hexane to give a yellow solid (3.98 g, 51%): mp 107-112°C; ^{1}H NMR ($CDCl_3$) 300 MHz 14.95 (s, 1H) 7.52 (dd, 1H) 7.23 (m, 1H) 6.97 (m, 1H) 5.07 (s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz -72.60 (s), -119.93 (m). Mass spectrum: M+=262.

Step 2. Preparation of 4-[1,4-dihydro-8-fluoro-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

4-Sulfonamidophenylhydrazine hydrochloride (1.54 g, 6.9 mmol) was added to a stirred solution of the diketone from Step 1 (1.62 g, 6.2 mmol) in ethanol (35 mL). The reaction was heated to reflux and stirred overnight (17.3 hours). The reaction mixture was filtered while hot to give the pyrazole as a white solid (1.09 g, 43%). Upon cooling, the filtrate yielded an additional 0.70 g (27%): mp 251-251.5°C; ^1H NMR (acetone-d_6) 300 MHz 8.17 (d, J=8.5 Hz, 2H) 7.91 (d, J=8.7 Hz, 2H) 7.11 (m, 2H) 6.87 (br s, 1H) 6.58 (dd, J=2.4Hz, 9.5Hz, 3H) 5.41 (s, 2H); ^{19}F NMR (acetone-d_6) 300 MHz -62.46 (s). High resolution mass spectrum Calc'd. for $C_{17}H_{11}F_4N_3O_3S$: 413.0457. Found: 413.0462.

EXAMPLE 6



4-[3-(Trifluoromethyl)-1H-benzofuro[3,2-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 2-(trifluoroacetyl)-3-coumaranone.

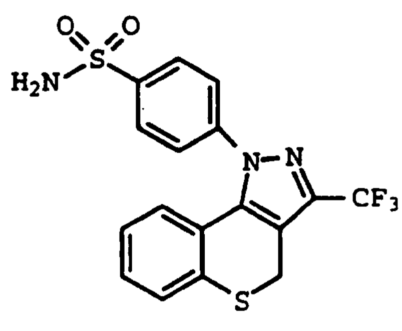
Ethyl trifluoroacetate (1.90 g, 14 mmol) was dissolved in ether (15 mL) and treated with sodium methoxide (25%) (3.67 g, 17 mmol). To the stirred solution was added 3-coumaranone (1.50 g, 11 mmol). The reaction was stirred at room temperature overnight

(19 hours) and treated with 3N HCl (8 mL). The organic layer was collected, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a reddish brown solid (2.19 g, 85%): mp 108-111°C; ^1H NMR ($CDCl_3$) 300 MHz 7.84 (d, J=8.1 Hz, 1H) 7.66 (m, 1H) 7.52 (d, J=8.7 Hz, 1H) 7.37 (m, 1H). Mass spectrum: M+H=231.

Step 2. Preparation of 4-[3-(trifluoromethyl)-1H-benzofuro[3,2-c]pyrazol-1-yl]benzenesulfonamide.

4-Sulfonamidophenylhydrazine hydrochloride (1.15 g, 5.0 mmol) was added to a stirred solution of the diketone from Step 1 (1.13 g, 4.9 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred for 2.5 hours. The reaction mixture was filtered to give the pyrazole as a brown solid (1.07 g, 57%): mp 190-195°C; ^1H NMR (acetone-d_6) 300 MHz 7.82-7.90 (m, 3H) 7.34-7.53 (m, 5H); ^{19}F NMR (acetone-d_6) 300 MHz -65.47 (s).

EXAMPLE 7



4-[1,4-Dihydro-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 3-(trifluoroacetyl)thio-4-chromanone.

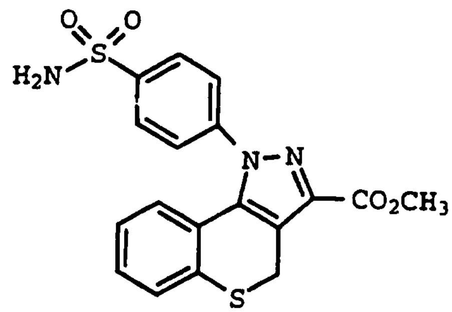
Ethyl trifluoroacetate (8.78 g, 62 mmol) was dissolved in ether (50 mL). To the stirred solution

was added sodium methoxide (14.35 g, 66 mmol) followed by thio-4-chromanone (9.43 g, 57 mmol) dissolved in ether (10mL). The reaction was stirred at room temperature overnight (17.8 hrs) and treated with 3N HCl (25 mL). The organic layer was collected, washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and recrystallized from ether/hexane to give a yellow solid (10.20 g, 68%): mp 75-79°C; ^{1}H NMR ($CDCl_3$) 300 MHz 15.62 (s, 1H) 7.99 (d, J=7.9Hz, 1H) 7.24-7.42 (m, 3H) 3.81 (s,2H); ^{19}F NMR ($CDCl_3$) 300 MHz -71.92 (s). Mass spectrum: M+= 260.

Step 2. Preparation of 4-[1,4-dihydro-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

4-Sulfonamidophenylhydrazine hydrochloride (5.74 g, 25.6 mmol) was added to a stirred solution of the diketone from Step 1 (6.04 g, 23.2 mmol) in ethanol (95 mL). The reaction was heated to reflux and stirred overnight (17.0 hours). The reaction mixture was filtered, and the filtrate cooled to 0°C and filtered to give the pyrazole as a yellow solid (4.42 g, 46%): mp 213-215°C; ^{1}H NMR (acetone-d_6) 300 MHz 8.09 (d, J=8.9 Hz, 2H) 7.75 (d, J=8.7 Hz, 2H) 7.53 (d, J=7.8Hz,1H) 7.29 (2d,1H) 7.07 (2d,1H) 6.94 (d, J=8.1Hz, 2H) 6.92 (br s, 1H) 4.09 (s, 2H); ^{19}F NMR (acetone-d_6) 300 MHz -62.22 (s). High resolution mass spectrum Calc'd. for $C_{17}H_{12}F_3N_3O_2S_2$: 411.0323. Found: 411.0330.

EXAMPLE 8



Methyl [1-[(4-aminosulfonyl)phenyl]-1,4-dihydro-[1]benzothiopyrano[4,3-c]pyrazol-3-yl]carboxylate

Step 1. Preparation of methyl-3-(1-oxo-2-carboxy)thiochroman-4-one.

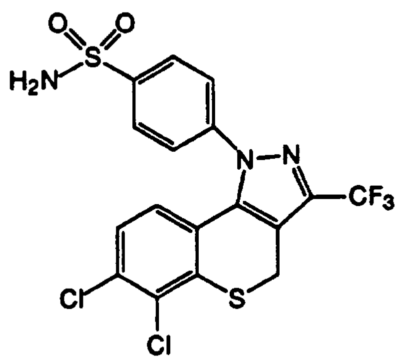
Thiochroman-4-one (9.84 g, 59.9 mmol) was added to dimethyl oxalate (8.54 g, 72.3 mmol) and methanol (75 mL). The reaction was treated with sodium methoxide (25% in methanol, 15.61 g, 72.2 mmol) and stirred at room temperature for 17.8 hours. The reaction was treated with 3N hydrochloric acid (30 mL) and filtered to give the diketone (13.58 g, 90%) as an orange solid: mp 94-97°C; ^{1}H NMR ($CDCl_3$) 300 MHz 15.94 (s, 1H) 8.01 (d, J=7.9 Hz, 1H) 7.24-7.39 (m, 3H) 4.11 (s, 2H) 3.94 (s, 3H). Mass spectrum: M+=250.

Step 2. Preparation of methyl 1-[4-(aminosulfonyl)phenyl]-1,4-dihydro-[1]benzothiopyrano[4,3-c]pyrazol-3-yl]carboxylate.

4-Sulfonamidophenylhydrazine hydrochloride (12.06 g, 53.9 mmol) was added to a stirred solution of the diketone from Step 1 (12.23 g, 48.9 mmol) in MeOH (250 mL). The reaction was heated to reflux and stirred for 6.5 hours. The reaction mixture was filtered, washed with MeOH and dried under vacuum to give the pyrazole as an orange solid (17.88 g, 91%): mp 265-269°C; ^{1}H NMR (DMSO-d_6) 300 MHz 7.97 (d, J=8.5

Hz, 2H) 7.69 (d, J=8.5 Hz, 2H) 7.58 (br s, 2H) 7.50 (d, J=7.9 Hz, 1H) 7.24 (t, J=7.7 Hz,1H) 7.04 (d, J=7.7 Hz, 1H) 6.76 (d, J=7.9 Hz, 1H) 4.21 (s, 2H) 3.86 (s, 3H). Mass spectrum: M+H=402.

EXAMPLE 9



4-[6,7-Dichloro-1,4-dihydro-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 3-(2,3-dichlorophenylthio)propanoic acid.

2,3-Dichlorothiophenol (4.94 g, 28 mmol) was added to acrylic acid (2.11 g, 29 mmol) and stirred at 50°C for 3 hours. The reaction mixture was poured into 10% Na_2CO_3 and extracted with ether. The aqueous layer was acidified with concentrated hydrochloric acid, extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the 3-(2,3-dichlorophenylthio)propanoic acid (3.88 g), contaminated with some acrylic acid, as a clear oil which was used without further purification in the next step.

Step 2. Preparation of 7,8-dichlorothiochroman-4-one.

The 3-(2,3-dichlorophenylthio)propanoic acid from Step 1 (3.88 g, 15 mmol) was dissolved in

trifluoroacetic acid (10 mL), treated with trifluoroacetic anhydride (5 mL) and stirred at room temperature for 68.2 hours. The reaction mixture was poured into 10% Na_2CO_3 (100 mL), extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow oil. The crude material was passed through a column of silica gel eluting with 40% ethyl acetate/hexane to give 7,8-dichlorothiochroman-4-one as a white solid (0.46 g, 13%): mp 93-102°C; ^1H NMR ($CDCl_3$) 300 MHz 7.99 (d, J=8.7 Hz, 1H) 7.27 (d, J=8.7 Hz, 1H) 3.25 (m, 2H) 2.97 (m, 2H). Mass spectrum: M+=233.

<u>Step 3. Preparation of 7,8-dichloro-3-(trifluoroacetyl)thiochroman-4-one.</u>

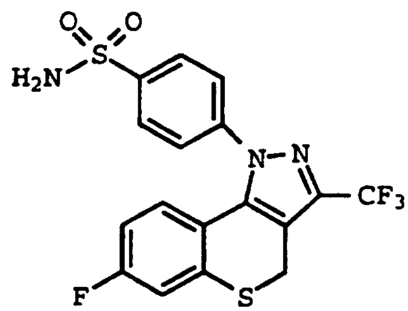
Ethyl trifluoroacetate (0.29 g, 2.0 mmol) was dissolved in ether (12 mL). To the stirred solution was added sodium methoxide (25%) (0.84 g, 3.9 mmol), followed by 7,8-dichlorothiochroman-4-one from Step 2 (0.42 g, 1.8 mmol). The reaction was stirred at room temperature overnight (19.4 hours) and treated with 3N hydrochloric acid. The organic layer was collected, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a brown oily solid which was used without purification in the next step.

<u>Step 4. Preparation of 4-[6,7-dichloro-1,4-dihydro-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide</u>.

4-Sulfonamidophenylhydrazine hydrochloride (0.32 g, 1.4 mmol) was added to a stirred solution of the diketone from Step 3 (0.44 g, 1.3 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred overnight (19.4 hours). The reaction mixture was filtered and the filtrate concentrated *in vacuo*, dissolved in ethyl acetate, washed with water and brine, dried over $MgSO_4$, reconcentrated *in vacuo*, and passed through a column of silica gel (hexane/ethyl

acetate) to give the pyrazole as a white solid (0.24 g, 38%): ^{1}H NMR (acetone-d_6) 300 MHz 8.08 (d, J=8.7 Hz, 2H) 7.77 (d, J=8.7 Hz, 2H) 7.27 (d, J=8.5Hz, 1H) 6.95 (d, J=8.5Hz,1H) 6.79 (br s, 2H) 4.23 (s, 2H); ^{19}F NMR (acetone-d_6) 300 MHz -62.25 (s). High resolution mass spectrum Calc'd. for $C_{17}H_{10}Cl_2F_3N_3O_2S_2$: 479.9622. Found: 479.9565.

EXAMPLE 10



4-[1,4-Dihydro-7-fluoro-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 3-(3-fluorophenylthio)propanoic acid.

3-Fluorothiophenol (5.39 g, 42 mmol) was added to acrylic acid (3.73 g, 52 mmol) and stirred at room temperature for 20.2 hours. The reaction mixture solidified, was dissolved in ether and extracted with 10% Na_2CO_3. The aqueous layer was acidified with concentrated hydrochloric acid, extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the 3-(3-fluorophenylthio)propanoic acid (6.75 g), contaminated with some acrylic acid, as a white solid which was used without further purification in the next step.

Step 2. Preparation of 7-fluorothiochroman-4-one.

The acid from Step 1 (6.75 g, 34 mmol) was dissolved in trifluoroacetic acid (20 mL), treated with trifluoroacetic anhydride (10 mL) and stirred at room temperature for 2.2 hours. The reaction mixture was poured into 10% Na_2CO_3 (100 mL), extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow oil which was passed through a column of silica gel with 20% ethyl acetate/hexane to give 7-fluorothiochroman-4-one as a white solid (2.09 g, 34%): mp 61-66°C; ^1H NMR ($CDCl_3$) 300 MHz 8.13 (m, 1H) 6.98 (m, 1H) 6.86 (m, 1H) 3.23 (m, 2H) 2.99 (m, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz -104.70 (m). Mass spectrum: M+H=183.

Step 3. Preparation of 7-fluoro-3-(trifluoroacetyl)thiochroman-4-one.

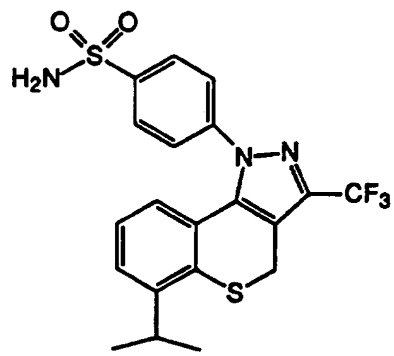
Ethyl trifluoroacetate (1.04 g, 7.3 mmol) was added to solution of 7-fluorothiochroman-4-one from Step 2 (1.24 g, 6.8 mmol) in ether (15 mL). The reaction was treated with 25% sodium methoxide (1.86 g, 8.6 mmol) and stirred at room temperature for 20.9 hours, then treated with 3N hydrochloric acid (10 mL). The organic layer was collected, washed with brine, dried over $MgSO_4$, concentrated *in vacuo*, and recrystallized from dichloromethane/isooctane to give the diketone as a yellow solid (0.58g, 31%): mp 84-89°C; ^1H NMR ($CDCl_3$) 300 MHz 15.65 (s, 1H) 8.03 (m, 1H) 7.08 (m,1H) 6.97 (m,1H) 3.83 (s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz -71.81 (s) -103.04 (m).

Step 4. Preparation of 4-[1,4-dihydro-7-fluoro-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

4-Sulfonamidophenylhydrazine hydrochloride (1.36 g, 6.1 mmol) was added to a stirred solution of the diketone from Step 3 (1.65 g, 5.9 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred overnight (15.2 hours). The reaction mixture was

filtered and the filtrate cooled in ice to give the pyrazole as a white solid (0.24 g, 38%): ^{1}H NMR (acetone-d_6) 300 MHz 8.09 (d, J=8.7 Hz, 2H) 7.76 (d, J=8.7 Hz, 2H) 7.38 (d, J=9.1Hz, 1H) 6.99 (m,1H) 6.88 (m, 1H) 6.80 (br s, 2H) 4.14 (s, 2H); ^{19}F NMR (acetone-d_6) 300 MHz: -62.25 (s) -112.68 (m). High resolution mass spectrum Calc'd. for $C_{17}H_{11}F_4N_3O_2S_2$: 429.0229. Found: 429.0205.

EXAMPLE 11



4-[1,4-Dihydro-6-isopropyl-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 3-(2-isopropylphenylthio)propanoic acid.

2-Isopropylthiophenol (4.77 g, 31 mmol) was placed in a flask with acrylic acid (2.37 g, 33 mmol) and stirred at room temperature for 71.8 hours. The reaction mixture solidified, was dissolved in ethyl acetate and extracted with 5% NaOH. The aqueous layer was acidified with concentrated hydrochloric acid, extracted with ethyl acetate, dried over $MgSO_4$, and concentrated *in vacuo* to give 3-(2-isopropylphenylthio)propanoic acid (6.85 g), contaminated with some acrylic acid, as a yellow

solid which was used without further purification in the next step.

Step 2. Preparation of 8-isopropylthiochroman-4-one.

3-(2-Isopropylphenylthio)propanoic acid from Step 1 (6.85 g, 30 mmol) was dissolved in trifluoroacetic acid (20 mL), treated with trifluoroacetic anhydride (12mL) and stirred at room temperature (64.2 hours). The reaction was concentrated *in vacuo*, and the residue dissolved in ethyl acetate, extracted with 5% NaOH, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a brown oil which was passed through a column of silica gel eluted with 12% ether/hexane to give 8-isopropylthiochroman-4-one as a brown oil (1.05 g, 17%): ^1H NMR ($CDCl_3$) 300 MHz 8.01 (d, J=7.0 Hz, 1H) 7.38 (d, J=7.5 Hz, 1H) 7.17 (t, J=7.8 Hz, 1H) 3.19 (m, 3H) 2.96 (m, 2H) 1.25 (d, J=7.0 Hz 6H).

Step 3. Preparation of 8-isopropyl-3-(trifluoroacetyl)thiochroman-4-one.

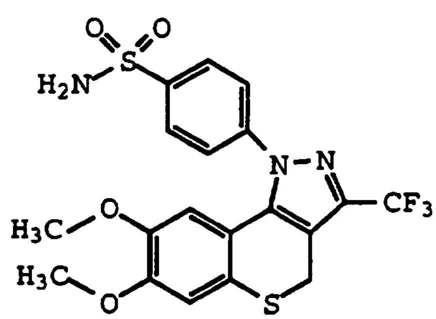
Ethyl trifluoroacetate (0.69 g, 4.9 mmol) was added to a solution of 2-isopropylthiochroman-4-one from Step 2 (0.97 g, 4.7 mmol) in ether (10 mL). The reaction was treated with 25% sodium methoxide (1.08 g, 5.0 mmol), stirred at room temperature for 18.2 hours and treated with 3N hydrochloric acid (5 mL). The organic layer was collected, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the diketone as a brown oil (0.80 g) which was used without further purification in the next step.

Step 4. Preparation of 4-[1,4-dihydro-6-isopropyl-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

4-Sulfonamidophenylhydrazine hydrochloride (0.69 g, 3.1 mmol) was added to a stirred solution of the

diketone from Step 3 (0.83 g, 2.7 mmol) in ethanol (10 mL). The reaction was heated to reflux, stirred overnight (16.1 hours) and concentrated *in vacuo*. The residue was dissolved in ethyl acetate washed with water, washed with brine, dried over $MgSO_4$, reconcentrated *in vacuo* and passed through a column of silica gel with 20% ethyl acetate/hexane to give the pyrazole as a brown solid (0.43 g, 35%): mp 183-186°C; ^1H NMR (acetone-d_6) 300 MHz 8.10 (d, J=8.7 Hz, 2H) 7.71 (d, J=8.5 Hz, 2H) 7.35 (d, J=7.9Hz, 1H) 7.04 (t, J=7.9 Hz, 1H) 6.79 (m, 3H) 4.04 (s, 2H) 3.46 (m, 1H) 1.28 (d, J=6.8 Hz, 6H); ^{19}F NMR (acetone-d_6) 300 MHz -62.19 (s) -112.68 (m). High resolution mass spectrum Calc'd. for $C_{20}H_{18}F_3N_3O_2S_2$: 453.0793. Found: 453.0848.

EXAMPLE 12



4-[1,4-Dihydro-7,8-dimethoxy-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 3-(3,4-dimethoxyphenylthio)propanoic acid.

3,4-Dimethoxythiophenol (5.00 g, 29 mmol) was placed in a flask with acrylic acid (2.27 g, 32 mmol) and stirred at room temperature for 22.4 hours. The reaction mixture solidified, was dissolved in ethyl acetate and extracted with 10% Na_2CO_3. The aqueous

layer was acidified with concentrated hydrochloric acid, extracted with ether, dried over $MgSO_4$, and concentrated *in vacuo* to give 3-(3,4-dimethoxyphenylthio)propanoic acid (5.39 g ,76%), contaminated with some acrylic acid, as a white solid which was used without further purification in the next step: mp 62-64°C; ^1H NMR ($CDCl_3$) 300 MHz 9.80 (br s, 1H) 7.01 (d, J=8.3 Hz, 1H) 6.98 (s, 1H) 6.82 (d, J=8.3 Hz, 1H) 3.87 (s, 3H) 3.86 (s, 3H) 3.06 (t, J=7.3 Hz, 2H) 2.63 (t, J=7.3 Hz, 2H). Mass spectrum: M+=242.

Step 2. Preparation of 6,7-dimethoxythiochroman-4-one.

The acid from Step 1 (5.23 g, 22 mmol) was dissolved in trifluoroacetic acid (20 mL), treated with trifluoroacetic anhydride (12 mL) and stirred at room temperature (10 minutes). The reaction was poured into 10% Na_2CO_3 (100 mL) and filtered to collect 6,7-dimethoxythiochromanone as a yellow solid (1.12 g, 23%). The filtrate was washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and recrystallized from ethyl acetate/hexane to give more 6,7-dimethoxythiochromanone (1.77 g, 37%) as an orange solid: mp 138-143°C; ^1H NMR ($CDCl_3$) 300 MHz 7.60 (s, 1H) 6.68 (s, 1H) 3.91 (s, 3H) 3.89 (s, 3H) 3.19 (m, 2H) 2.93 (m, 3H). Mass spectrum: M+=224.

Step 3. Preparation of 6,7-dimethoxy-3-trifluoroacetylthiochroman-4-one.

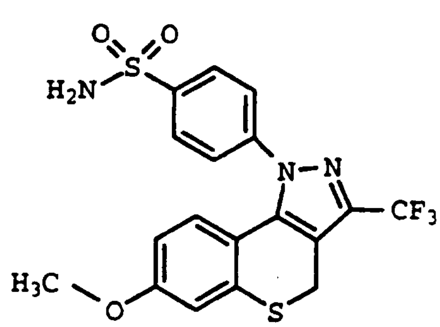
Ethyl trifluoroacetate (0.84 g, 5.9 mmol) was dissolved in tetrahydrofuran (20 mL), and treated with 25% sodium methoxide (1.68 g, 7.8 mmol). To the stirred solution was added 6,7-dimethoxythiochroman-4-one from Step 2 (1.12 g, 5.0 mmol). The reaction was stirred at room temperature for 87.5 hours, treated with 3N HCl (25 mL) and filtered to give an

orange solid (1.04 g, 65%): mp 148-151°C; ^1H NMR ($CDCl_3$) 300 MHz 16.05 (s, 1H), 7.48 (s, 1H) 6.78 (s, 1H) 3.94 (s, 3H) 3.92 (s, 3H) 3.83 (s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz -71.06 (s). Mass spectrum: M+H= 321.

Step 4. Preparation of 4-[1,4-dihydro-7,8-dimethoxy-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

4-Sulfonamidophenylhydrazine hydrochloride (0.76 g, 3.4 mmol) was added to a stirred solution of the diketone from Step 3 (1.00 g, 3.1 mmol) in ethanol (20 mL). The reaction was heated to reflux and stirred overnight (15.5 hours). The reaction mixture was filtered and the filtrate concentrated *in vacuo*, dissolved in ethyl acetate, washed with water and brine, dried over $MgSO_4$, reconcentrated *in vacuo*, and recrystallized from ethyl acetate/isooctane to give the pyrazole as a yellow solid (0.72 g, 49%): mp 164-168°C; ^1H NMR (acetone-d_6) 300 MHz 8.13 (d, J=8.7 Hz, 2H) 7.77 (d, J=8.5 Hz, 2H) 7.06 (s, 1H) 6.82 (br s, 2H) 6.36 (s, 1H) 4.04 (s, 2H) 3.85 (s, 3H) 3.85 (s, 3H); ^{19}F NMR (acetone-d_6) 300 MHz -62.20(s). High resolution mass spectrum Calc'd. for $C_{19}H_{16}F_3N_3O_4S_2$: 471.0534. Found: 471.0534.

EXAMPLE 13



4-[1,4-Dihydro-7-methoxy-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Srep 1. Preparation of 3-(3-methoxyphenylthio)propanoic acid.

3-Methoxythiophenol (5.70 g, 41 mmol) was placed in a flask with acrylic acid (2.36 g, 33 mmol) and stirred at room temperature for 113.8 hours. The reaction mixture was dissolved in ether and extracted with 10% Na_2CO_3. The aqueous layer was acidified with concentrated HCl, extracted with ether, dried over $MgSO_4$, and concentrated *in vacuo* to give the 3-(3-methoxyphenylthio)propanoic acid (2.55 g , 37%) as a white solid: mp 39-42°C; ^1H NMR ($CDCl_3$) 300 MHz 7.21 (m, 1H) 6.91 (m, 2H) 6.77 (d, J=8.3 Hz, 1H) 3.79 (s, 3H) 3.16 (t, J=7.5 Hz, 2H) 2.68 (t, J=7.3 Hz, 2H).

Step 2. Preparation of 7-methoxythiochroman-4-one.

The acid from Step 1 (2.55 g, 12 mmol) was dissolved in trifluoroacetic acid (10 mL), treated with trifluoroacetic anhydride (5 mL) and stirred at room temperature (10 minutes). The reaction was poured into 10% Na_2CO_3 (60 mL), extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a red oil which was passed through a column of silica gel with 50% ether/hexane to give 7-methoxythiochroman-4-one as an orange solid (1.18 g, 51%): mp 49-51°C; ^1H NMR ($CDCl_3$) 300 MHz 8.06 (d, J=8.9 Hz, 1H) 6.72 (m, 2H) 3.83 (s, 3H) 3.20 (m, 2H) 2.95 (m, 2H). Mass spectrum: M+H=195.

Step 3. Preparation of 7-methoxy-3-(trifluoroacetyl)thiochroman-4-one.

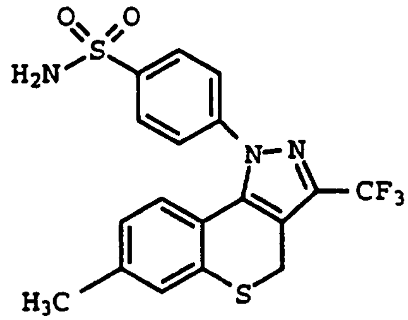
7-Methoxythiochroman-4-one from Step 2 (1.13 g, 5.8 mmol) and ethyl trifluoroacetate (0.87 g, 6.1

mmol) were dissolved in ether (15 mL), treated with 25% sodium methoxide (2.13 g, 9.9 mmol), stirred at room temperature for 23.0 hours, and treated with 3N HCl. The organic layer was collected, washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and recrystallized from dichloromethane/isooctane to give the diketone as a yellow solid (0.60 g, 35%): mp 93-98°C; ^1H NMR ($CDCl_3$) 300 MHz 15.92 (s, 1H) 7.96 (d, J=8.9 Hz, 1H) 6.82 (m, 2H) 3.87 (s, 3H) 3.82 (s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz -71.43 (s). Mass spectrum: M+H=291.

Step 4. Preparation of 4-[1,4-dihydro-7-methoxy-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

4-Sulfonamidophenylhydrazine hydrochloride (0.46 g, 2.1 mmol) was added to a stirred solution of the diketone from Step 3 (0.57 g, 2.0 mmol) in ethanol (5 mL). The reaction was heated to reflux and stirred overnight (21.5 hrs). The reaction mixture was filtered while hot to give the pyrazole as a yellow solid (0.63 g, 72%): mp 201-206°C; ^1H NMR (acetone-*d6*) 300 MHz 8.08 (d, J=8.7 Hz, 2H) 7.73 (d, J=8.7 Hz, 2H) 7.09 (d, J=2.6 Hz, 1H) 6.84 (d, J=8.7 Hz, 1H) 6.80 (br s,1H) 6.66 (dd, J=2.6 Hz J=8.9 Hz , 1H) 4.07 (s, 2H) 3.83 (s, 3H); ^{19}F NMR (acetone-*d6*) 300 MHz -62.24 (s). High resolution mass spectrum Calc'd. for $C_{18}H_{14}F_3N_3O_3S_2$: 441.0429. Found: 441.0457.

EXAMPLE 14



4-[1,4-Dihydro-7-methyl-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 3-(3-methylphenylthio)propanoic acid.

3-Thiocresol (9.71 g, 78 mmol) was placed in a flask with acrylic acid (5.65 g, 78 mmol) and stirred at room temperature for 62.9 hours. The reaction mixture solidified and was dissolved in ether and extracted with 10% Na_2CO_3. The aqueous layer was acidified with concentrated hydrochloric acid, extracted with ether, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the 3-(3-dimethylphenylthio)propanoic acid (10.13 g , 66%) contaminated with some acrylic acid as a white solid, which was used without further purification in the next step.

Step 2. Preparation of 7-methylthiochroman-4-one.

3-(3-Methylphenylthio)propanoic acid from Step 1 (10.12 g, 52 mmol) was dissolved in trifluoroacetic acid (20 mL), treated with trifluoroacetic anhydride (10 mL) and stirred at room temperature for 1.9 hours. The reaction was poured into 10% Na_2CO_3 (100 mL), extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an

orange oil which was passed through a column of silica gel eluting with 8% ether/hexane to give 7-methylthiochroman-4-one (2.97 g, 32%) as a yellow oil: ^{1}H NMR ($CDCl_3$) 300 MHz 7.97 (d, J=8.1 Hz, 1H) 7.06 (s, 1H) 6.97 (d, J=7.7 Hz, 1H) 3.17 (m, 2H) 2.95 (m, 2H) 2.31 (s, 3H). Mass spectrum: M+H=179.

<u>Step 3. Preparation of 7-methyl-3-(trifluoroacetyl)thiochroman-4-one.</u>

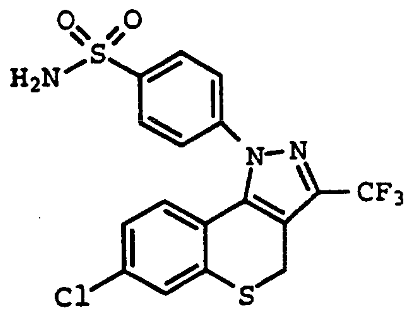
7-Methylthiochroman-4-one from Step 2 (2.92 g, 16 mmol) and ethyl trifluoroacetate (2.45 g, 17 mmol) were dissolved in ether (20 mL), treated with 25% sodium methoxide (4.60 g, 21 mmol), stirred at room temperature for 15.0 hours and treated with 3N hydrochloric acid (15 mL). The organic layer was collected, washed with brine, dried over $MgSO_4$, concentrated *in vacuo*, and recrystallized from dichloromethane/isooctane to give the diketone as a yellow solid (3.05g, 68%): mp 68-72°C; ^{1}H NMR ($CDCl_3$) 300 MHz 15.73 (s, 1H) 7.89 (d, J=8.1 Hz, 1H) 7.17 (s, 1H) 7.09 (d, J=8.1 Hz, 1H) 3.80 (s, 2H) 2.37 (s, 3H); ^{19}F NMR ($CDCl_3$) 300 MHz -71.75 (s). Mass spectrum: M+H=275.

<u>Step 4. Preparation of 4-[1,4-dihydro-7-methyl-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.</u>

4-Sulfonamidophenylhydrazine hydrochloride (1.21 g, 5.4 mmol) was added to a stirred solution of the diketone from Step 3 (1.41 g, 5.1 mmol) in ethanol (20 mL). The reaction was heated to reflux and stirred overnight (15.8 hours). The reaction mixture was filtered and the filtrate concentrated *in vacuo*, dissolved in ethyl acetate, washed with water and brine, dried over $MgSO_4$, reconcentrated *in vacuo*, and recrystallized from ethyl acetate/isooctane to give the pyrazole as a yellow solid (1.14 g, 52%): mp 251-

252°C; ^1H NMR (acetone-d_6) 300 MHz 8.08 (d, J=8.7 Hz, 2H) 7.73 (d, J=8.7 Hz, 2H) 7.36 (s, 1H) 6.79 (m, 4H) 4.06 (s, 2H) 2.29 (s, 3H); ^{19}F NMR (acetone-d_6) 300 MHz -62.22(s). High resolution mass spectrum Calc'd. for $C_{18}H_{14}F_3N_3O_2S_2$: 425.0480. Found: 425.0470.

EXAMPLE 15



4-[7-Chloro-1,4-dihydro-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 3-(3-chlorophenylthio)propanoic acid

Acrylic acid (2.66 g, 37 mmol) and 3-chlorothiophenol (4.85 g, 34 mmol) were dissolved in ether (15 mL) and stirred at room temperature for 88.0 hours. The reaction mixture solidified, was dissolved in ether and extracted with 5% NaOH. The aqueous layer was acidified with concentrated hydrochloric acid, extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the 3-(3-chlorophenylthio)propanoic acid (2.20 g, 34%): ^1H NMR (acetone-d_6) 300 MHz 7.33-7.40 (m, 3H) 7.24 (m, 1H) 3.25 (t, J=7.1 Hz, 2H) 2.67 (t, J=7.1 Hz, 2H). Mass spectrum: M+H=217.

Step 2. Preparation of 7-chlorothiochroman-4-one.

3-(3-Chlorophenylthio)propanoic acid from Step 1 (2.18 g, 10 mmol) was dissolved in trifluoroacetic acid (10 mL), treated with trifluoroacetic anhydride (6 mL) and stirred at room temperature for 67.8 hours. The reaction was concentrated *in vacuo* and the residue dissolved in dichloromethane, extracted with 5% NaOH, dried over $MgSO_4$, and reconcentrated *in vacuo* to give a brown oil. The crude oil was passed through a column of silica gel with 10% ether/hexane to give a mixture of 7-chlorothiochroman-4-one and 5-chlorothiochroman-4-one as a yellow oil (1.30 g) which was carried on to the next step without further purification.

Step 3. Preparation of 7-chloro-3-(trifluoroacetyl)thiochroman-4-one.

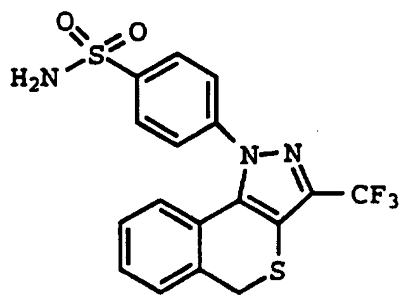
Ethyl trifluoroacetate (1.02 g, 7.2 mmol) was placed in a round bottom flask and dissolved in ether (10 mL). To the stirred solution was added 25% sodium methoxide (1.80 g, 8.3 mmol) followed by 7-chlorothiochroman-4-one from Step 2 (1.30 g, 6.5 mmol). The reaction was stirred at room temperature overnight (17.3 hrs) and treated with 3N hydrochloric acid (5 mL). The organic layer was collected, washed with brine, dried over $MgSO_4$, concentrated *in vacuo*, and recrystallized from ether/hexane to give the diketone (0.61 g, 32%) as a yellow solid: mp 64-71°C; ^1H NMR ($CDCl_3$) 300 MHz 15.53 (s, 1H) 7.92 (d, J=8.5 Hz, 1H) 7.36 (s, 1H) 7.25 (d, J=8.7 Hz, 1H) 3.82 (s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz -71.97 (s). Mass spectrum: M+=294.

Step 4. Preparation of 4-[7-chloro-1,4-dihydro-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

4-Sulfonamidophenylhydrazine hydrochloride (0.43 g, 1.9 mmol) was added to a stirred solution of the

diketone from Step 3 (0.55 g, 1.9 mmol) in ethanol (6 mL). The reaction was heated to reflux and stirred for 18.9 hours. The reaction mixture was cooled and filtered to give the pyrazole as a yellow solid (0.15 g, 18%): mp 237-238°C; ^{1}H NMR (acetone-d_6) 300 MHz 8.09 (d, J=8.7 Hz, 2H) 7.77 (d, J=8.7 Hz, 2H) 7.59 (d, J=2.0 Hz,1H) 7.10 (dd, J=8.5 Hz J=2.0Hz, 1H) 6.96 (d, J=8.5 Hz , 1H) 6.81 (br s, 2H) 4.14 (s, 2H); ^{19}F NMR (acetone-d_6) 300 MHz -62.25(s). High resolution mass spectrum Calc'd. for $C_{17}H_{11}ClF_3N_3O_2S_2$: 444.9933. Found: 444.9874.

EXAMPLE 16



4-[1,5-Dihydro-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 3-(trifluoroacetyl)isothiochroman-4-one.

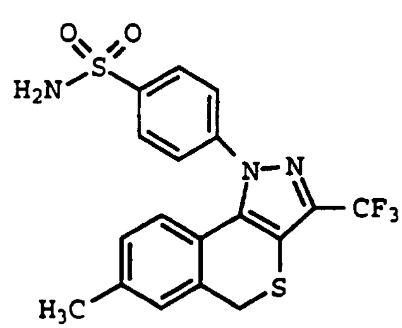
Ethyl trifluoroacetate (3.67 g, 25.8 mmol) was dissolved in tetrahydrofuran (15 mL) and treated with 25% sodium methoxide (6.46 g, 29.9 mmol) followed by a solution of isothiochroman-4-one (4.15 g, 25.3 mmol) in tetrahydrofuran (15 mL). The reaction was stirred at room temperature for 70.8 hours and treated with 3N hydrochloric acid (10 mL). The organic layer was collected, washed with brine, dried over $MgSO_4$, concentrated *in vacuo*, and passed through

a column of silica gel eluting with 40% ethyl acetate/hexane to give a brown solid (5.40 g, 82%): ^1H NMR ($CDCl_3$) 300 MHz 15.30 (s, 1H) 7.99 (d, J=7.9 Hz, 1H) 7.54 (m, 1H) 7.43 (m, 1H) 7.23 (m, 1H) 3.81 (s, 3H).

Step 2. Preparation of 4-[1,5-dihydro-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

4-Sulfonamidophenylhydrazine hydrochloride (0.81 g, 3.6 mmol) was added to a stirred solution of the diketone from Step 1 (0.83 g, 3.2 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred 2.1 hours. The reaction mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and with brine, dried over $MgSO_4$, reconcentrated *in vacuo*, and passed through a column of silica gel with 40% ethyl acetate to give the pyrazole (0.15 g, 11%): mp 230-232°C; ^1H NMR (acetone-d_6) 300 MHz 8.09 (d, J=8.7 Hz, 2H) 7.85 (d, J=8.9 Hz, 2H) 7.53 (d, J=7.7Hz, 1H) 7.40 (t, J=7.5 Hz,1H) 7.21 (t, J=7.7 Hz,1H) 6.93 (d, J=7.9 Hz, 1H) 6.79 (br s ,2H) 4.16 (s, 2H); ^{19}F NMR (acetone-d_6)) 300 MHz -62.94(s). High resolution mass spectrum Calc'd. for $C_{17}H_{12}F_3N_3O_2S_2$: 411.0323. Found: 411.0324.

EXAMPLE 17



4-[1,5-Dihydro-7-m thyl-3-(trifluoromethyl)-[2]benzothiopyran [4,3-c]pyrazol-1-yl]benz nesulfonamide

<u>Step 1. Preparation of S-(3-methylbenzyl)-isothiouronium chloride.</u>

Thiourea (26.19 g, 344 mmol) was added to a solution of α-chloro-*m*-xylene (48.21 g, 343 mmol) in methanol (50 mL). The reaction was heated to reflux and additional methanol (10 mL) was added to dissolve all of the thiourea. After 64.3 hours, the reaction was filtered and dried under vacuum to give a white solid (68.15 g, 92%): mp 182-186°C; ^{1}H NMR (DMSO-d_6) 300 MHz 9.34 (br s, 4H) 7.22 (m, 3H) 7.12 (m, 1H) 4.48 (s, 2H) 2.27 (s, 3H).

<u>Step 2. Preparation of 3-(3-methylphenylthio)propanoic acid.</u>

A 250 mL flask was charged with the thiouronium salt from Step 1 (10.99 g, 51 mmol), sodium chloroacetate (8.86 g, 76 mmol), ethanol (95 mL) and water (10 mL). After heating to reflux, a solution of NaOH (9.05 g, 226 mmol) in water (50 mL) was added to the reaction dropwise over seven minutes. After stirring for 3.6 hours. the reaction was acidified with concentrated hydrochloric acid, extracted with ether, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a white solid (9.95 g, 100%): mp 73-75.5°C; ^{1}H NMR ($CDCl_3$) 300 MHz 7.16 (m, 4H) 3.83 (s, 2H) 3.12 (s, 2H) 2.35 (s, 3H). Mass spectrum: M+=196.

<u>Step 3. Preparation of 7-methylisothiochroman-4-one.</u>

The acid from Step 2 (6.06 g, 31 mmol) was dissolved in trifluoroacetic acid (11 mL), treated with trifluoroacetic anhydride (5 mL) and stirred at room temperature for 0.33 hours. The reaction was

poured into 10% Na_2CO_3 (100 mL), extracted with ether, washed with brine, dried over $MgSO_4$, concentrated *in vacuo*, and recrystallized from ether/hexane to give 7-chloroisothiochroman-4-one (2.25 g, 41%) as a white solid: mp 79.5-82°C; ^1H NMR ($CDCl_3$) 300 MHz 7.97 (d, J=8.1 Hz, 1H) 7.17 (d, J=8.1 Hz, 1H) 7.00 (s, 1H) 3.87 (s, 2H) 3.52 (s, 2H) 2.37 (s, 3H). Mass spectrum: M+H=179.

Step 4. Preparation of 7-methyl-3-(trifluoroacetyl)isothiochroman-4-one.

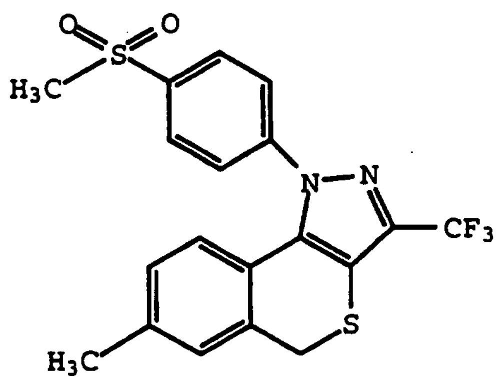
Ethyl trifluoroacetate (1.80 g, 12.7 mmol) was placed in a round bottom flask and dissolved in ether (10 mL). To the stirred solution was added 25% sodium methoxide (3.90 g, 18.0 mmol) followed by 7-chloroisothiochroman-4-one from Step 3 (2.25 g, 12.6 mmol) dissolved in ether (10 mL) and tetrahydrofuran (10 mL). The reaction was stirred at room temperature for 24.6 hours and treated with 3N hydrochloric acid. The organic layer was collected, washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and passed through a column of silica gel with 20% ether/hexane to give the diketone (1.93 g, 56%) as a brown solid: ^1H NMR ($CDCl_3$) 300 MHz 15.45 (s, 1H) 7.88 (d, J=8.1 Hz, 1H) 7.25 (d, J=8.1 Hz, 1H) 7.06 (s, 1H) 3.77 (s, 2H) 2.43 (s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz: -72.76 (s). Mass spectrum: M+H=275.

Step 5. Preparation of 4-[1,5-dihydro-7-methyl-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

4-Sulfonamidophenylhydrazine hydrochloride (1.68 g, 7.5 mmol) was added to a stirred solution of the diketone from Step 4 (1.93 g, 7.0 mmol) in ethanol (15 mL). The reaction was heated to reflux and stirred for 15.2 hours. The reaction mixture was

concentrated *in vacuo* and the residue dissolved in ethyl acetate, washed with water and with brine, dried over $MgSO_4$, reconcentrated *in vacuo* and recrystallized from ethyl acetate/isooctane to give the pyrazole as a brown solid (1.48 g, 49%): mp 253-255°C; ^1H NMR (acetone-d_6) 300 MHz 8.08 (d, J=8.7 Hz, 2H) 7.83 (d, J=8.7 Hz, 2H) 7.35 (s, 1H) 7.02 (d, J=8.1 Hz,1H) 6.78 (m, 3H) 4.11 (s, 2H) 2.34 (s, 3H); ^{19}F NMR (acetone-d_6) 300 MHz -62.94(s). High resolution mass spectrum Calc'd. for $C_{18}H_{14}F_3N_3O_2S_2$: 426.0558. Found: 426.05554.

EXAMPLE 18



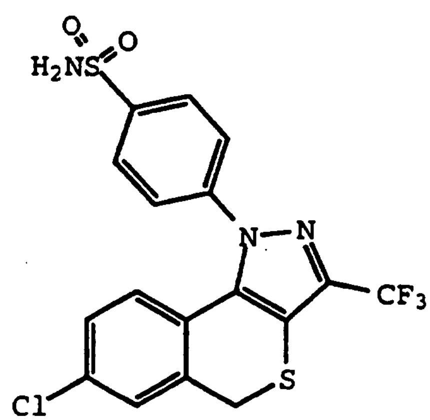
1,5-Dihydro-1-[4-(methylsulfonyl)phenyl]-7-methyl-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazole

Step 1. Preparation of 1-[4-methylsulfonylphenyl]-7-methyl-3-(trifluoromethyl)-1,5-dihydro-[2]benzothiopyrano[4,3-c]pyrazole.

4-(Methylsulfonyl)phenylhydrazine (1.23 g, 6.6 mmol) was converted to the hydrochloride salt by stirring with a 4N solution of hydrochloric acid in dioxane (10 mL) for 25 minutes. The dioxane was removed *in vacuo*, and the 4-(methylsulfonyl)phenylhydrazine hydrochloride was combined with the diketone (Example 17, Step 4) (1.12

g, 2.9 mmol) and ethanol (20 mL), heated to reflux and stirred for 15.5 hours. The reaction mixture was filtered while hot and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and with brine, dried over $MgSO_4$, reconcentrated *in vacuo*, and passed through a column of silica gel eluting with 12% ethyl acetate/hexane to give the pyrazole (0.31 g, 18%) as a yellow solid: mp 207-209°C; ^1H NMR (acetone-d_6) 300 MHz 8.14 (d, J=8.7 Hz, 2H) 7.92 (d, J=8.9 Hz, 2H) 7.35 (s, 1H) 7.35 (d, J=8.1 Hz, 1H) 6.83 (d, J=7.9 Hz, 1H) 4.11 (s, 2H) 3.23 (s, 3H) 2.34 (s, 3H); ^{19}F NMR (acetone-d_6) 300 MHz -62.97 (s). High resolution mass spectrum Calc'd. for $C_{19}H_{15}F_3N_2O_2S_2$: 424.0527. Found: 424.0524.

EXAMPLE 19



4-[7-Chloro-1,5-dihydro-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

<u>Step 1. Preparation of S-(3-chlorobenzyl)-isothiouronium chloride.</u>

3-Chlorobenzyl chloride (24.2 g, 0.15 mol) and thiourea (11.4 g, 0.15 mol) were dissolved in methanol (70 mL) and heated to reflux for 16 hours.

The reaction was cooled to room temperature and a precipitate formed. Ether (150 mL) was added to complete the precipitation of compound. The crystals were isolated by filtration and washed with ether (100 mL). After drying *in vacuo*, 31.9 g (90%) of pure S-(3-chlorobenzyl)-isothiouronium chloride was obtained: ^1H NMR (CD_3OD) δ = 4.43p (s, 2H), 7.36p (s, 3H), 7.47p (s, 1H).

<u>Step 2. Preparation of 3-chlorobenzylmercaptoacetic acid</u>

S-(3-Chlorobenzyl)-isothiouronium chloride from Step 1 (11.86 g, 50 mmol) and chloroacetic acid (7.1 g, 75 mmol) were dissolved in ethanol (100 ml) and heated to 80°C in a 4-neck flask equipped with nitrogen inlet, condenser and addition funnel. A solution of NaOH (10 g) in H_2O (100 mL) and ethanol (50 mL) was added dropwise over 1 hour to this hot solution. The reaction was heated to 100°C for 4 hours. The reaction was cooled to room temperature, acidified with concentrated hydrochloric acid (45 mL) and extracted with ether (500 mL). The organic layer was washed with brine (300 ml), dried over $MgSO_4$ and concentrated *in vacuo* to yield 10.84 g (100%) of 3-chlorobenzylmercaptoacetic acid which was used without further purification: ^1H NMR ($CDCl_3$) δ = 3.08p (s, 2H), 3.80p (s, 2H), 7.23p (m, 3H), 7.34p (s, 1H), 9.07p (broad s, 1H).

<u>Step 3. Preparation of 7-chloroisothiochroman-4-one.</u>

3-Chlorobenzylmercaptoacetic acid from Step 2 (3.35 g) was dissolved in trifluoroacetic acid (50 mL). Trifluoroacetic acid anhydride (25 mL) was added and the reaction stirred at reflux, under a nitrogen atmosphere for 16 hours. The solution was carefully poured into 10% Na_2CO_3 solution (500 mL) which was stirring vigorously. The organics were

extracted into ether (500 mL) and washed with brine (300 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting brown solid was purified by silica gel chromatography eluting with a 0-10% gradient of ethyl acetate in hexane to yield 7-chloroisothiochroman-4-one (1.57 g, 51%): ^1H NMR ($CDCl_3$) δ = 3.49p (d, 2H, J = 0.8 Hz), 3.8p (s, 2H), 7.16p (m, 1H), 7.3p (dd, 1H, J = 2.0, 8.4 Hz), 7.96p (d, 1H, J = 8.5 Hz).

Step 4. Preparation of 7-chloro-3-(trifluoroacetyl)isothiochroman-4-one.

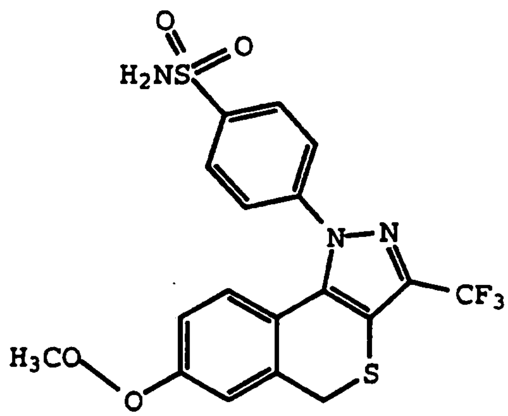
7-Chloroisothiochroman-4-one from Step 3 (0.3 g, 1.5 mmol) was dissolved in tetrahydrofuran (15 mL) and cooled to -78°C. A solution of sodium bistrimethylsilyl amide (1.5 mL of a 1.0M tetrahydrofuran solution) was added and the reaction stirred for 0.5 hours at -78°C. Trifluoroacetyl imidazole (0.21 mL, 1.8 mmol) was added and the reaction was warmed to room temperature and stirred under a nitrogen atmosphere for 16 hours. 1N Hydrochloric acid (100 mL) was added to the reaction followed by extraction with ether (150 mL). The organics were washed with brine (75 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting yellow oil was used in the next step without further purification.

Step 5. Preparation of 4-[7-chloro-1,5-dihydro-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

A mixtrue of the diketone from Step 4 (1.51 mmol) and 4-sulphonamidophenylhydrazine hydrochloride (0.41 g, 1.8 mmol) was dissolved in ethanol (50 mL) and heated to reflux for 16 hours. The reaction was concentrated *in vacuo* and the resulting solid was dissolved in ethyl acetate (200 mL). The organics were washed with water (200 mL) and with brine (150

mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was chromatographed on silia gel eluting with a gradient of ethyl acetate (from 10 - 50%) in hexane to yield pure tricyclic pyrazole (0.25 g, 40%): mp 241-242°C; ^1H NMR (acetone-d_6) δ = 4.18p (s, 2H), 6.79p (s, 2H), 6.94p (d, 1H, J = 8.5 Hz), 7.26p (dd, 1H, J = 2.2, 8.4 Hz), 7.6p (d, 1H, J = 2.2 Hz), 7.83p (dd, 2H, J = 2.1, 6.9 Hz), 8.1p (dd, 2H, J = 2.1, 6.7 Hz); ^{19}F NMR (acetone-d_6) δ -62.94p (s, 3F).

EXAMPLE 20



4-[1,5-Dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

<u>Step 1. Preparation of S-(3-methoxyphenylmethyl)-isothiouronium chloride.</u>

A solution of 3-methoxybenzyl chloride (15.65 g, 0.1 mol) and thiourea (7.6 g, 0.1 mol) were dissolved in 40 mL of ethanol and heated to reflux for 16 hours, during this time the isothiouronium salt crystallized. The thiouronium chloride was isolated by filtration and recrystallized from ether and ethanol (21.85 g, 94%, mp 172.5-174.0°C). This material was used directly in the next step.

Step 2. Preparation of 3-methoxybenzylmercaptoacetic acid

The thiouronium chloride from Step 1 (20.00 g, 86 mmol) and chloroacetic acid (11.07 g, 95 mmol) were dissolved in ethanol (100 mL) and heated to 80°C in a 4-neck flask equipped with nitrogen inlet, condenser and addition funnel. A solution of NaOH (10 g) in water (100 mL) and ethanol (50 mL) was added dropwise over 1 hour to the hot solution. The reaction was heated to 100°C for 4 hours. The reaction was cooled to room temperature, acidified with concentrated hydrochloric acid (45 mL), and extracted with ether (500 mL). The organic layer was washed with brine (300 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield an oil that was vacuum distilled to provide 16.41 g (90%) of pure acid: bp 160-170°C at 0.2 mm; ^1H NMR ($CDCl_3$/300 MHz) 3.1p (s, 2H), 3.8p (s, 3H), 3.82p (s, 2H), 6.8p (m, 1H), 6.91p (s, 1H), 6.96p (m, 1H), 7.23p (t, 1H, J = 7.7 Hz), 8.33p (broad s, 1H), 11.1(brs, 1H).

Step 3. Preparation of 7-methoxyisothiochroman-4-one

3-methoxybenzylmercaptoacetic acid from Step 2 (10.82 g) was dissolved in trifluoroacetic acid (50 mL). Trifluoroacetic acid anhydride (25 mL) was added and the reaction stirred under a nitrogen atmosphere for 0.25 hours. At this time, TLC showed no starting material. The solution was carefully poured into 10% Na_2CO_3 solution (500 mL) which was stirring vigorously. The organics were extracted into ether (500 mL) and washed with brine (300 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting brown solid was purified by silica gel chromatography eluting with 20% ethyl acetate in hexane to yield 7-methoxyisothiochroman-4-one (4.84 g, 49%): ^1H NMR ($CDCl_3$) δ = 3.48p (t, 2H, J = 0.8

Hz), 3.83p (s, 3H), 3.84p (s, 2H), 6.6p (d, 1H, J = 2.4 Hz), 6.83p (dd, 1H, J = 2.4, 8.9 Hz), 8.0p (d, 1H, J = 8.9 Hz).

Step 4. Preparation of 7-methoxy-3-(trifluoroacetyl)-isothiochroman-4-one.

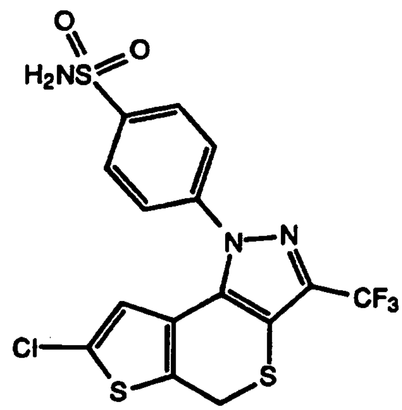
7-Methoxyisothiochroman-4-one from Step 3 (0.58 g, 3.0 mmol) was dissolved in tetrahydrofuran (30 mL) and cooled to -78°C. A solution of sodium bistrimethylsilylamide (3.0 mL of a 1.0 M tetrahydrofuran solution) was added and the reaction stirred for 0.5 hours at -78°C. Trifluoroacetyl imidazole (0.41 mL, 3.6 mmol) was added and the reaction was warmed to room temperature and stirred under a nitrogen atmosphere for 16 hours. At this time, 1N hydrochloric acid (200 mL) was added to the reaction followed by extraction with ether (250 mL). The organics were washed with brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting yellow oil (0.42 g, 48%) was used without further purification.

Step 5. Preparation of 4-[1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

A solution of the dione from Step 4 (0.42 g, 1.4 mmol) and 4-sulphonamidophenylhydrazine hydrochloride (0.42 g, 1.8 mmol) were dissolved in ethanol (50 mL) and heated to reflux for 16 hours. The reaction was concentrated *in vacuo* and the resulting solid was dissolved in ethyl acetate (200 mL). The organics were washed with H_2O (200 mL) followed by brine (150 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was chromatographed on silica gel eluting with a gradient of ethyl acetate (from 20-50%) in hexane to yield pure tricyclic pyrazole (0.25 g, 41%): mp 268-270°C; ^1H NMR (acetone-d_6) δ = 3.84p

(s, 3H), 4.12p (s, 2H), 6.8p (m, 3H), 7.1p (d, 1H, J = 2.4 Hz), 7.81p (d, 2H, J = 6.6 Hz), 7.82p (s, 2H), 8.08p (dd, 2H, J = 1.9, 6.6 Hz); ^{19}F NMR (acetone-d_6) δ = -62.9p (s, 3F).

EXAMPLE 21



4-[7-Chloro-1,5-dihydro-3-trifluoromethyl-thieno[3',2':4,5]thiopyrano[3,2-c]pyrazol-1-yl]benzenesulfonamide

<u>Step 1. Preparation of S-(5-chloro-2-thienylmethyl)-isothiouronium chloride.</u>

2-Chloro-5-(chloromethyl)thiophene (14.5 g, 87 mmol) and thiourea (6.6 g, 87 mol) were dissolved in methanol (30 mL) and heated to reflux for 16 hours. The reaction was cooled to room temperature and a precipitate formed. Ether (150 mL) was added to complete the precipitation of compound. The crystals were isolated by filtration and washed with ether (100 mL). After drying *in vacuo*, 19.0 g (90%) of pure S-(5-chloro-2-thienylmethyl)-isothiouronium chloride were obtained: ^1H NMR (CD_3OD) δ = 4.83p (s, 2H), 6.87p (d, 1H, J = 3.8 Hz), 6.96p (d, 1H, J = 3.2 Hz).

Step 2. Preparation of 5-chloro-2-thienylmethylmercaptoacetic acid.

The compound from Step 1 (12.16 g, 50 mmol) and chloroacetic acid (7.1 g, 75 mmol) were dissolved in ethanol (100 mL) and heated to 80°C in a 4-neck flask equipped with nitrogen inlet, condenser and addition funnel. A solution of NaOH (10 g) in water (100 mL) and ethanol (50 mL) was added dropwise over 1 hour to the hot solution. The reaction was heated to 100°C for 4 hours. The reaction was cooled to room temperature, acidified with concentrated hydrochloric acid (45 mL) and extracted with ether (500 mL). The organic layer was washed with brine (300 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield 11.14 g (100%) of pure acid which was used without further purification: ^1H NMR ($CDCl_3$) δ = 3.2p (s, 2H), 3.98p (s, 2H), 6.73p (d, 1H, J = 3.6 Hz), 6.77p (d, 1H, J = 3.8 Hz).

Step 3 Preparation of 6-chloro-5,6-dihydro-4H-thieno[2,3-b]thiopyran-4-one

The acid from Step 2 (4.45 g) was dissolved in trifluoroacetic acid (45 mL). Trifluoroacetic acid anhydride (20 mL) was added and the reaction was stirred under a nitrogen atmosphere for 0.25 hours. At this time, TLC showed no starting material. The solution was carefully poured into 10% Na_2CO_3 solution (600 mL) which was stirring vigorously. The organics were extracted into ethyl acetate (500 mL), washed with brine (300 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting brown solid was purified by SiO_2 chromatography eluting with 10% ethyl acetate in hexane to yield of pure intermediate (2.5 g, 61%): ^1H NMR ($CDCl_3$) δ = 3.33p (d, 2H, J = 0.6 Hz), 3.78p (s, 2H), 7.1p (s, 1H).

Step 4 Preparation of 6-chloro-5,6-dihydro-3-trifluoroacetyl-4H-thieno[2,3-b]thiopyran-4-one

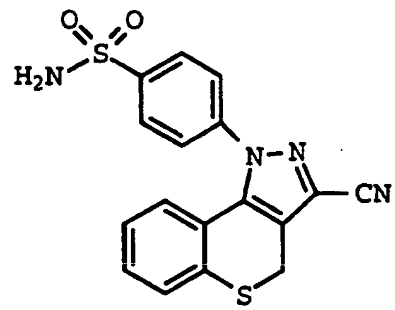
The compound from Step 3 (1.03 g, 5.0 mmol) was dissolved in tetrahydrofuran (50 mL) and cooled to -78°C. A solution of sodium bistrimethylsilylamide (5.0 mL of a 1.0 M tetrahydrofuran solution) was added and the reaction stirred for 0.75 hours at -78°C. Trifluoroacetyl imidazole (0.68 mL, 6.0 mmol) was added and the reaction was warmed to room temperature and stirred under a nitrogen atmosphere for 16 hours. At this time, 1N hydrochloric acid (300 mL) was added to the reaction followed by extraction with ether (350 mL). The organics were washed with brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting yellow oil was used without further purification.

Step 5 Preparation of 4-[7-chloro-1,5-dihydro-3-trifluoromethyl-thieno[3',2':4,5]thiopyrano[3,2-c]pyrazol-1-yl]benzenesulfonamide

The compound from Step 4 (5.5 mmol) and 4-sulphonamidophenylhydrazine hydrochloride (1.47 g, 6.6 mmol) were dissolved in ethanol (100 mL) and heated to reflux for 16 hours. The reaction was concentrated *in vacuo* and the resulting solid dissolved in ethyl acetate (300 mL). The organics were washed with water (300 mL) followed by brine (200 mL) and were then dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was chromatographed on silica gel eluting with a gradient of ethyl acetate (from 20 - 40%) in hexane. This product was first crystallized from ethyl acetate and isooctane, then from ethanol and water to yield pure 4-[7-chloro-1,5-dihydro-3-trifluoromethyl-thieno[3',2':4,5]thiopyrano[3,2-c]pyrazol-1-yl]benzenesulfonamide [0.35 g, 16% from Step 2]: mp 218-220°C (dec); ^1H NMR ($CDCl_3$) δ = 4.0p (s, 2H),

6.27p (s, 2H), 7.32p (s, 1H), 7.61(d, 2H, J = 7.0 Hz), 8.02p (d, 2H, J = 7.0 Hz); ^{19}F NMR (acetone-d_6) δ = -59.25p (s, 3F).

EXAMPLE 22



1-[4-(Aminosulfonyl)phenyl]-1,4-dihydro-[1]benzothiopyrano[4,3-c]pyrazol-3-carbonitrile

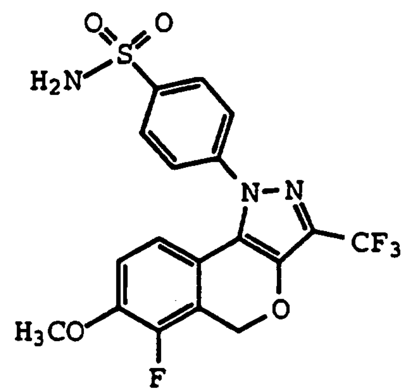
Step 1. Preparation of 1-[4-(aminosulfonyl)phenyl]-1,4-dihydro-[1]benzothiopyrano[4,3-c]pyrazol-3-carboxamide.

The compound from Example 8 (11.31 g, 28.3 mmol) was placed in a 500 mL flask with methanol (200 mL), anhydrous ammonia was bubbled through the solution, the flask was capped and allowed to stand. After 14 days the reaction was concentrated *in vacuo* and recrystallized from ethyl acetate to give the carboxamide as yellow solid (10.14 g, 93%): mp 238-242°C; ^1H NMR (acetone-d_6) 300 MHz 8.07 (d, J=8.7 Hz, 2H) 7.72 (d, J=8.7 Hz, 2H) 7.49 (d, J=7.9 Hz, 1H) 7.30 (br s, 1H) 7.23 (dd, 1H) 7.02 (dd, 1H) 6.91 (d, J=7.9 Hz, 1H) 6.80 (br s, 2H) 6.75 (br s, 1H) 4.28 (s, 2H). Mass spectrum: M+H=387.

Step 2. Preparation of 1-[4-(aminosulfonyl)phenyl]-1,4-dihydro-[1]benzothiopyrano[4,3-c]pyrazol-3-carbonitrile

Dimethylformamide (10 mL) (DMF) was placed in a 250 mL flask and cooled to 0°C. Oxalyl chloride (2 mL, 23 mmol) was added and stirred for 15 minutes. A solution of the product from Step 1 (3.34 g, 9 mmol) in DMF (13 mL) was added and the reaction was stirred for 0.8 hours, treated with pyridine (3.8 mL, 47 mmol), poured into 3N hydrochloric acid (30 mL) and filtered to give a solid (2.86 g). The filtrate was extracted with dichloromethane, washed with 3N hydrochloric acid and with saturated $NaHCO_3$, dried over $MgSO_4$, concentrated *in vacuo*, combined with the previously collected solid, purified by flash chromatography on silica gel eluting with 1% methanol/dichloromethane, and recrystallized from dichloromethane/isooctane to give a solid (2.44 g, mp 220-222°C) which was the DMF adduct of the desired product. The DMF adduct (2.44 g) was dissolved in dioxane (18 mL) and treated with a 4N solution of hydrochloric acid in dioxane (10 mL). The solution was stirred at room temperature for 7.25 hours, heated to reflux for 42 hours, filtered, and concentrated *in vacuo*. The residue was dissolved in methylene chloride, washed wtih water, dried over $MgSO_4$, and reconcentrated *in vacuo* to give a brown foam (2.43 g) which was a mixture of the desired product and its adduct with DMF. The mixture was purified by flash chromatography on silica gel eluting with 40% ethyl acetate/hexane to give the desired product as a white solid (0.62 g, 19%): mp 211-213°C; ^1H NMR (acetone-d_6) 300 MHz 8.10 (d, J=8.5 Hz, 2H) 7.76 (d, J=8.5 Hz, 2H) 7.54 (d, J=7.7 Hz, 1H) 7.30 (dd, 1H) 7.07 (dd, 1H) 6.94 (d, J=8.1 Hz, 1H) 6.82 (br s, 2H) 4.12 (s, 2H). High resolution mass Calc'd. for $C_{17}H_{12}N_4O_2S_2$: 368.0402. Found: 368.0368.

EXAMPLE 23



4-[1,4-Dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 2-fluoro-3-methoxyphenyl)-3-oxo-propanoic acid.

A solution of 2-fluoro-3-methoxybenzyl alcohol (1.57 g, 9.22 mmol), chloroacetic acid (1.72 g, 18.2 mmol), and ethanol (0.04 mL) in 20 mL of anhydrous tetrahydrofuran was added to a mixture of sodium hydride (2.29 g, 95.2 mmol) in 10 mL of anhydrous tetrahydrofuran dropwise over 10 minutes at 0°C. The cooling bath was removed and the solution warmed to room temperature and then was heated to reflux for 14 hours. The solution was cooled to room temperature, acidified with 3N hydrochloric acid, and extracted with ether. The ethereal phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to provide a yellow solid (2.04 g, 100%) that was used directly in the next step: ^1H NMR ($CDCl_3$/300 MHz) 8.60 (brs, 1H), 7.08-6.93 (m, 3H), 4.72 (d, J=1.4 Hz, 2H), 4.17 (s, 2H), 3.88 (s, 3H); ^{19}F NMR ($CDCl_3$/282 MHz) -141.50 (t). Mass spectrum M+Li = 221.

<u>Step 2. Preparation of 7-methoxy-8-fluoro-isochroman-4-one.</u>

A solution of 2-fluoro-3-methoxyphenyl)-3-oxo-propanoic acid from Step 1 (1.96 g, 8.6 mmol) in 4 mL of trifluoroacetic acid and 2 mL of trifluoroacetic anhydride was stirred at room temperature for 1 hour. The solution was concentrated *in vacuo*, the residue dissolved in ether, and the ethereal solution was washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a solid that was purified by flash chromatography to provide 0.37 g (32%) of the desired ketone. The aqueous phase from the $NaHCO_3$ was acidified, extracted with ether, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to provide 1.13 g, of recovered 2-fluoro-3-methoxyphenyl)3-oxo-propanoic acid: mp 112-118°C; ^1H NMR ($CDCl_3$/300 MHz) 7.86 (dd, J=8.66, 1.41 Hz, 1H), 7.00 (apparent t, J=8.26 Hz, 1H), 4.96 (s, 2H), 4.31 (S, 2H), 3.97 (S, 3H); ^{19}F NMR ($CDCl_3$/282 MHz) -142.2 (d). Mass spectrum M^+ = 196.

<u>Step 3. Preparation of 7-methoxy-8-fluoro-3-(trifluoroacetyl)isochroman-4-one</u>.

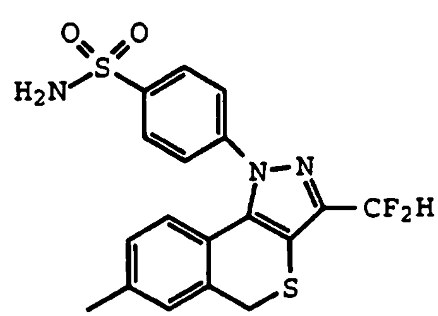
A solution of 7-methoxy-8-fluoro-isochroman-4-one from Step 2 (370 mg, 1.76 mmol) and ethyl trifluoroacetate (290 mg, 2.04 mmol) in 8 mL of anhydrous tetrahydrofuran was treated with a solution of 25% sodium methoxide in methanol (570 mg, 2.64 mmol). The solution was stirred at room temperature for 16 hours, treated with excess 3N hydrochloric acid, and extracted with ether. The ethereal extract was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford 450 mg (88%) of pure 7-methoxy-8-fluoro-3-(trifluoroacetyl)isochroman-4-one which was used

directly in the next step without further purification.

Step 4. Preparation cf 4-[6-fluoro-1,4-dihydro-7-methoxy-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

7-Methoxy-8-fluoro-3-(trifluoroacetyl)isochroman-4-one from Step 3 (450 mg, 1.47 mmol) and 4-sulfonamidophenylhydrazine hydrochloride (430 mg, 1.92 mmol) were dissolved in 5 mL of anhydrous ethanol and heated to reflux for 45 minutes. The solution was concentrated *in vacuo* and the residue was dissolved in ethyl acetate. The solution was washed with 3N hydrochloric acid, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was crystallized from a mixture of isooctane and ethyl acetate to afford 4-[1,4-dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide as a white solid (200 mg, 30%): mp 289.5-291.0°C; ^{1}H NMR (acetone d_6/300 MHz) 8.12 (d, J=8.4 Hz, 2H), 7.90 (d, J=8.5 Hz. 2H), 7.07 (dd, J=8.7, 8.5 Hz, 1H), 6.83 (br s, 2H), 6.75 (d, J=8.7 Hz, 1H), 5.45 (s, 2H), 3.90 (s, 3H); ^{19}F NMR (acetone d_6/282 MHz) -62.51 (s), -140.97 (d). High resolution mass spectrum Calc'd. for $C_{18}H_{13}F_4N_3O_4S$: 443.0563. Found: 443.0570.

EXAMPLE 24



4-[3-(Difluoromethyl)-1,5-dihydro-7-methyl-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benz nesulfonamide

Step 1. Preparation of S-(3-methylbenzyl)-isothiouronium chloride.

Thiourea (26.19 g, 344 mmol) was added to a solution of α-chloro-m-xylene (48.21 g, 343 mmol) in methanol (50 mL). The reaction was heated to reflux and additional methanol (10 mL) was added to dissolve all of the thiourea. After 64.3 hours, the reaction was filtered and dried *in vacuo* to give a white solid (68.15 g, 92%): mp 182-186 °C. ^{1}H NMR (DMSO-d_6 300 MHz) 9.34 (br s, 4H) 7.22 (m, 3H) 7.12 (m, 1H) 4.48 (s, 2H) 2.27 (s, 3H).

Step 2. Preparation of 3-(3-methylphenylthio)propanoic acid.

The thiouronium salt from Step 1 (10.99 g, 51 mmol) was added to sodium chloroacetate (8.86 g, 76 mmol), ethanol (95 mL), and water (10 mL). After heating to reflux, a solution of NaOH (9.05 g, 226 mmol) in water (50 mL) was added to the reaction dropwise over seven minutes. After stirring for 3.6 hours, the reaction was acidified with concentrated hydrochloric acid, extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a white solid (9.95 g, 100%): mp 73-75.5 °C. ^{1}H NMR ($CDCl_3$ 300 MHz) 7.16 (m, 4H) 3.83 (s, 2H) 3.12 (s, 2H) 2.35 (s, 3H). Mass spectrum: M+=196.

Step 3. Preparation of 7-methylisothiochroman-4-one.

The acid from Step 2 (6.06 g, 31 mmol) was dissolved in trifluoroacetic acid (11 mL), treated with trifluoroacetic anhydride (5 mL) and stirred at room temperature for 0.33 hour. The reaction was poured into 10% Na_2CO_3 (100 mL) and extracted with ether, washed with brine, dried over $MgSO_4$, concentrated *in vacuo*, and recrystallized from ether/hexane to give 7-

chloroisothiochroman-4-one (2.25 g, 41%) as a white solid: mp 79.5-82 °C. ^{1}H NMR ($CDCl_3$ 300 MHz) 7.97 (d, J=8.1 Hz, 1H) 7.17 (d, J=8.1 Hz, 1H) 7.00 (s, 1H) 3.87 (s, 2H) 3.52 (s, 2H) 2.37 (s, 3H). Mass spectrum: M+H=179.

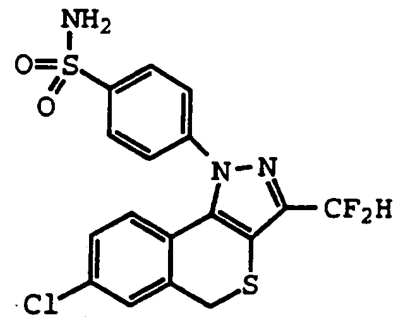
Step 4. Preparation of 7-methyl-3-(difluoroacetyl)isothiochroman-4-one.

Ethyl difluoroacetate (1.27 g, 10.3 mmol) was dissolved in ether (100 mL). To the stirred solution was added 25 weight % sodium methoxide (2.47 ml, 10.8 mmol) followed by 7-methylisothiochroman-4-one from Step 3 (1.83 g, 10.27 mmol) dissolved in ether (50 mL). The reaction was stirred at room temperature for 16 hours and treated with 1N hydrochloric acid. The organic layer was collected, washed with brine, dried over $MgSO_4$, concentrated *in vacuo*. The crude product was used without further purification.

Step 5. Preparation of 4-[3-(difluoromethyl)-1,5-Dihydro-7-methyl-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

4-Sulfonamidophenylhydrazine hydrochloride (2.67 g, 11.9 mmol) was added to a stirred solution of the diketone from Step 4 (2.35 g, 9.17 mmol) in ethanol (75 mL). The reaction was heated to reflux and stirred for 16 hours. The reaction was concentrated *in vacuo* and the residue was dissolved in ethyl acetate, washed with water and brine, dried over $MgSO_4$, concentrated *in vacuo*, and crystallized from ethyl acetate/isooctane to give the pyrazole as a white solid (1.98 g, 53%): ^{1}H NMR (acetone-d_6 300 MHz) 2.34 (s, 3H), 4.06 (s. 2H), 6.8 (m, 3H), 6.96 (t, 1H, J = 54 Hz), 7.0 (m, 1H), 7.34(s, 1H), 7.78 (d, 2H, J = 8.66 Hz), 8.06 (d, 2H, J = 8.66 Hz). ^{19}F NMR (acetone-d_6 282 MHz) -115.5, d, J = 54 Hz.

EXAMPLE 25



4-[7-Chloro-3-(difluoromethyl)-1,5-dihydro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of S-(3-chlorobenzyl)-isothiouronium chloride.

3-Chlorobenzyl chloride (24.2 g, 0.15 mol) and thiourea (11.4 g, 0.15 mol) were dissolved in methanol (70 mL) and heated to reflux for 16 hours. The reaction was cooled to room temperature and a precipitate formed. Ether (150 mL) was added to complete the precipitation of product. The crystals were isolated by filtration and washed with ether (100 mL). After drying *in vacuo*, 31.9 g (90%) of pure S-(3-chlorobenzyl)- isothiouronium chloride was obtained: ^{1}H NMR (CD_3OD) 4.43(s, 2H) 7.36(s, 3H) 7.47(s, 1H).

Step 2. Preparation of 3-chlorobenzylmercaptoacetic acid.

S-(3-Chlorobenzyl)-isothiouronium chloride from Step 1 (11.86 g, 50 mmol) and chloroacetic acid (7.1 g, 75 mmol) were dissolved in ethanol (100 ml) and heated to 80 °C in a 4-neck flask equipped with nitrogen inlet, condenser and addition funnel. A solution of NaOH (10 g) in H_2O (100 mL) and ethanol (50 mL) was added dropwise over 1 hour to this hot solution. The reaction was then heated to 100 °C for 4 hours. The reaction was cooled to room temperature, acidified with concentrated hydrochloric acid (45 mL) and

extracted with ether (500 mL). The organic layer was washed with brine (300 ml), dried over $MgSO_4$ and concentrated *in vacuo* to yield 10.84 g (100%) of 3-chlorobenzylmercaptoacetic acid which was used without further purification: ^1H NMR ($CDCl_3$ 300 MHz) 3.08 (s, 2H) 3.80 (s, 2H) 7.23 (m, 3H) 7.34 (s, 1H), 9.07 (broad s, 1H).

Step 3. Preparation of 7-chloroisothiochroman-4-one.

3-Chlorobenzylmercaptoacetic acid (Step 2) (3.35 g) was dissolved in trifluoroacetic acid (50 mL). Trifluoroacetic acid anhydride (25 mL) was added and the reaction was heated at reflux, under nitrogen, for 16 hours. The solution was carefully poured into 10% Na_2CO_3 solution (500 mL) which was stirring vigorously. The organics were extracted into ether (500 mL) and washed with brine (300 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting brown solid was purified by SiO_2 chromatography, eluting with a 0-10% gradient of ethyl acetate in hexane to yield 7-chloroisothiochroman-4-one, (1.57 g, 51%): ^1H NMR ($CDCl_3$ 300 MHz) 3.49 (d, 2H, J = 0.8 Hz), 3.8 (s, 2H), 7.16 (m, 1H), 7.3 (dd, 1H, J = 2.0, 8.4 Hz), 7.96 (d, 1H, J = 8.5 Hz).

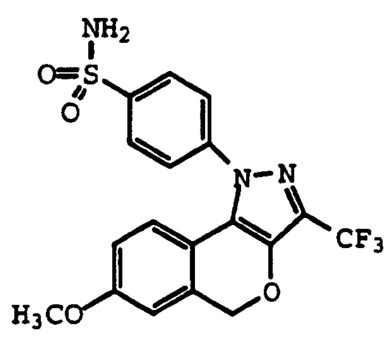
Step 4. Preparation of 7-chloro-3-(difluoroacetyl) isothiochroman-4-one.

Ethyl difluoroacetate (1.37 g, 11.1 mmol) was dissolved in diethyl ether (100 mL). To the stirred solution was added 25 weight % sodium methoxide (2.7 ml, 11.7 mmol), followed by 7-chloroisothiochroman-4-one (Step 3) (2.2 g, 11.1 mmol) dissolved in diethyl ether (50 mL). The reaction was stirred at room temperature for 16 hours, then treated with 1N hydrochloric acid. The organic layer was collected, washed with brine, dried over $MgSO_4$, concentrated *in vacuo*. The crude product was used without further purification.

Step 5. Preparation of 4-[7-chloro-3-(difluoromethyl)-1,5-dihydro-[2]benzothiopyrano [4,3-c]pyrazol-1-yl]benzenesulfonamide.

A mixture of the product from Step 4 (11.1 mmol) and 4-sulphonamidophenylhydrazine hydrochloride (3.2 g, 14.4 mmol) were dissolved in ethanol (100 mL) and heated to reflux for 16 hours. The reaction was concentrated *in vacuo* and the resulting solid was dissolved in ethyl acetate (200 mL). The organics were washed with water (200 mL), brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was chromatographed on SiO_2 eluting with a gradient of ethyl acetate (from 10-50%) in hexane to yield pure tricyclic pyrazole (1.9 g, 40%): ^1H NMR (acetone-d_6 300 MHz) 4.13 (s, 2H), 6.8 (s, 2H), 6.9 (m, 1H), 7.0 (t, 1H, J = 78 Hz), 7.25 (m, 1H), 7.6 (s, 1H), 7.8 (d, 2H, J = 8.66 Hz), 8.1 (d, 2H, J = 8.66 Hz). ^{19}F NMR (acetone-d_6 282 MHz) -115.5 (d, J = 78 Hz).

EXAMPLE 26



4-[1,5-Dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 3-(3-methoxybenzyloxy)acetic acid.

A suspension of sodium hydride (5.49 g, 0.217 mol) in 80 mL of anhydrous THF was cooled to 0 °C and treated with a solution of 3-methoxybenzyl alcohol (10.0 g, 72.4 mmol) and chloroacetic acid (10.26 g, 0.108 mol) in 80 mL of THF

over ca. 0.25 hour. The solution was stirred at 0 °C for 2 hours and then warmed to room temperature for 14 hours. The solution was cooled to 0 °C, treated with 50 mL of 6N HCl and extracted with dichloromethane. The dichloromethane solution was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford 13.48 g (95%) of pure 3-(3-methoxybenzyloxy)acetic acid that was used directly in the next step: ^1H NMR ($CDCl_3$ 300 MHz) 7.31-7.26 (m, 1H), 6.94-6.85 (m, 3H), 4.63 (s, 2H), 4.15 (s, 2H), 3.82 (s, 3H).

<u>Step 2. Preparation of 7-methoxyisochroman-4-one.</u>

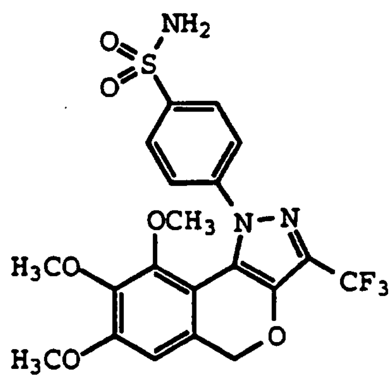
A solution of 3-(3-methoxybenzyloxy)acetic acid (Step 1) (6.50 g, 33.1 mmol) in 20 mL of trifluoroacetic acid was treated with trifluoroacetic anhydride (5.15 g, 36.4 mmol) and stirred at room temperature for 0.75 hour. The solution was concentrated *in vacuo* and the residue was purified by flash chromatography over silica gel eluting with 10% ethyl acetate in hexane to afford 3.96 g (67%) of 7-methoxyisochroman-4-one: ^1H NMR ($CDCl_3$/300 MHz) 8.01 (d, J=8.66 Hz, 1H), 6.90 (dd, J=8.66, 2.42 Hz, 1H), 6.65 (d, J=2.42 Hz, 1H), 4.84 (s, 2H), 4.32 (s, 2H), 3.87 (s, 3H).

<u>Step 3. Preparation of 4-[1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.</u>

A mixture of 7-methoxyisochroman-4-one (3.96 g, 22.2 mmol) and ethyl trifluoroacetate (2.90 mL, 5.8 mmol) was dissolved in 30 mL of diethyl ether and treated with a solution of 25% sodium methoxide in methanol (5.8 mL, 26.7 mmol). The solution was stirred at room temperature for 1 hour. The solution was diluted with 1N HCl and extracted with ethyl acetate, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a solid. The crude reaction product was dissolved in 50 mL of ethanol and treated with 4-sulfonamidophenylhydrazine hydrochloride (5.47 g, 24.4 mmol). This solution was

heated to reflux for 3.5 hours, cooled to room temperature, diluted with 100 mL of 1N HCl. After cooling the solution to 0 °C for *ca*. 0.5 hour, crystals of pure 4-[1,5-dihydro-7-methoxy-3- (trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide formed that were isolated by filtration and dried *in vacuo* to afford 7.56 g (80%): mp 275 °C (dec). ^{1}H NMR ($CDCl_3$ 300 MHz) 7.91 (d, J=8.66 Hz, 2H), 7.54 (d, J=8.66 Hz, 2H), 6.69-6.54 (m, 5H), 5.07 (s, 2H), 3.63 (s, 3H). ^{19}F NMR ($CDCl_3$ 282 MHz) -62.01(s). Anal. calc'd. for $C_{18}H_{14}F_3N_3O_4S$: C, 50.82; H, 3.32; N, 9.88; S, 7.54. Found: C, 50.93; H, 3.38; N, 9.94; S, 7.57.

EXAMPLE 27



4-[1,5-Dihydro-7,8,9-trimethoxy-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

<u>Step 1. Preparation of 3-(3,4,5-trimethoxybenzyloxy)acetic acid.</u>

A suspension of sodium hydride (10.2 g, 0.403 mol) in 80 mL of anhydrous THF was cooled to 0 °C and treated with a solution of 3,4,5-trimethoxybenzyl alcohol (8.00 g, 40.4 mmol) and chloroacetic acid (7.63 g, 80.7 mmol) in 80 mL of THF over 1 hour. The solution was stirred at 0 °C for 1 hour and heated to reflux for 14 hours. The solution was cooled to 0 °C, treated with 30 mL of methanol, 10 mL of water, and then the solution was extracted with dichloromethane. The dichloromethane solution was washed

with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford 10.4 g, 100% of pure 3-(3-methoxybenzyloxy)acetic acid that was used directly in the next step.

Step 2. Preparation of 6,7,8-trimethoxyisochroman-4-one.

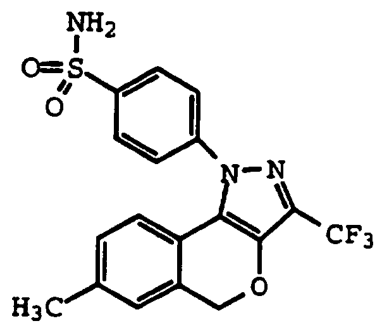
A solution of 3-(3,4,5-trimethoxybenzyloxy)acetic acid (Step 1) (10.0 g, 39 mmol) in 30 mL of trifluoroacetic acid was treated with trifluoroacetic anhydride (15 mL) and stirred at room temperature for 20 minutes. The solution was concentrated *in vacuo* and used directly in the next step without purification: ^1H NMR ($CDCl_3$ 300 MHz) 6.56 (s, 2H), 4.58 (s, 2H), 4.16 (s, 2H), 3.86 (s, 6H), 3.83 (s, 3H).

Step 3. Preparation of 4-[1,5-dihydro-7,8,9-trimethoxy-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

The crude product from Step 2 was dissolved in 40 mL of diethyl ether, mixed with ethyl trifluoroacetate (3.35 mL, 28.1 mmol), treated with 25% sodium methoxide in methanol (10 mL, 30.7 mmol) and stirred at room temperature for 16 hours. The solution was diluted with 30 mL of 1N HCl, extracted with ethyl acetate, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford 6.3 g of an oil. The oil was dissolved in ethanol, mixed with 4-sulfonamidophenylhydrazine hydrochloride (6.3 g, 28.2 mmol) and the solution was heated to reflux for 16 hours. The solution was cooled to room temperature, diluted with 30 mL of 1N HCl, extracted with ethyl acetate, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a solid that showed two major components by TLC. The material was purified by flash chromatography over silica gel, eluting with 20% ethyl acetate in hexane to afford 877 mg of material that was crystallized from hexane to afford 400 mg (2%) of pure 4-[1,5-dihydro-6,7,8-trimethoxy-3- (trifluoromethyl)-

[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide from 3-(3,4,5-trimethoxybenzyloxy)acetic acid: mp 130 °C. ^{1}H NMR ($CDCl_3$ 300 MHz) 7.99 (d, J=8.66 Hz, 2H), 7.63 (d, J=8.66 Hz, 2H), 6.65 (s, 1H), 5.13 (s, 2H), 4.83 (s, 2H), 3.92 (s, 3H), 3.76 (s, 3H), 3.26 (s, 3H). ^{19}F NMR ($CDCl_3$ 282 MHz) -62.10(s). High resolution mass spectrum calc'd. For $C_{20}H_{18}F_3N_3O_6S$: 485.0885. Found: 485.0779.

EXAMPLE 28



4-[1,5-Dihydro-7-methyl-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 3-(3-methylbenzyloxy)acetic acid.

A suspension of sodium hydride (1.96 g, 75.6 mmol) in 80 mL of anhydrous THF was cooled to 0°C and treated with a solution of 3-methylbenzyl alcohol (3.16 g, 25.9 mmol) and chloroacetic acid (3.67 g, 38.8 mmol) in 80 mL of THF over *ca.* 1 hour. The solution was stirred at 0 °C for 1.5 hours and heated to reflux for 16 hours. The solution was cooled to 0 °C, treated with 50 mL of 6N HCl and extracted with dichloromethane. The dichloromethane solution was washed with brine, dried over anhyd. $MgSO_4$, filtered and concentrated *in vacuo* to afford 2.67 g (57%) of pure 3-(3-methylbenzyloxy)acetic acid that was used directly in the next step. ^{1}H NMR ($CDCl_3$ 300 MHz) 7.28-7.12 (m, 4H), 4.62 (s, 2H), 4.14 (s, 2H), 2.36 (s, 3H).

Step 2. Preparation of 7-methylisochroman-4-one.

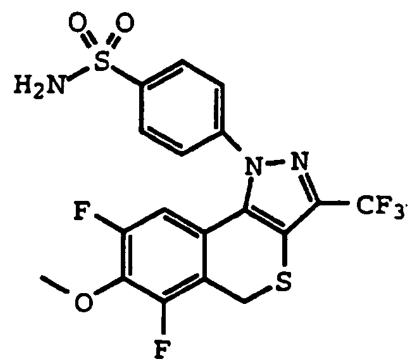
A solution of 3-(3-methylbenzyloxy)acetic acid (Step 1) (2.67 g, 14.8 mmol) in 25 mL of trifluoroacetic acid was treated with trifluoroacetic anhydride (2.5 mL, 17.8 mmol) and stirred at room temperature for 16 hours. The solution was concentrated *in vacuo* and the residue was dissolved in dichloromethane, washed with sat. aq. $NaHCO_3$, brine, dried over anhyd. $MgSO_4$, filtered and concentrated *in vacuo* to afford an oil, 1.45 g, 60%. Examination of the NMR spectrum revealed that the product was a 3:1 mixture of 7-methylisochroman-4-one:5-methylisochroman-4-one. Flash chromatography of the mixture eluting with 10% ethyl acetate in hexane provided the desired isomer 7-methylisochroman-4-one [^1H NMR ($CDCl_3$ 300 MHz) 7.94 (d, J=7.86 Hz, 1H), 7.22 (d, J=7.86 Hz, 1H), 7.02 (s, 1H), 4.85 (s, 2H), 4.35 (s, 2H), 2.42 (s, 3H)].

<u>Step 3. Preparation of 4-[1,5-dihydro-7-methyl-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.</u>

The product from Step 2 was dissolved in 20 mL of diethyl ether, mixed with ethyl trifluoroacetate (0.12 mL, 9.5 mmol), treated with 25% sodium methoxide in methanol (2.2 mL, 10.4 mmol) and stirred at room temperature for 16 hours. The solution was diluted with 10 mL of 1N HCl, extracted with ethyl acetate, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford an oil. The oil was dissolved in ethanol, mixed with 4-sulfonamidophenylhydrazine hydrochloride (2.12 g, 9.5 mmol) and the solution was heated to reflux for 3 hours. The solution was cooled to room temperature and diluted with 30 mL of 0.5N HCl. The solution was chilled in an ice bath, whereupon crystals formed that were isolated by filtration and dried *in vacuo* to afford 1.27 g, 36% of pure product: mp 285 °C (dec). ^1H NMR ($CDCl_3$ 300 MHz) 8.05 (d, J=8.66 Hz, 2H), 7.70 (d, J=8.66 Hz, 2H), 7.05 (s, 1H), 6.97 (d, J=7.96 Hz, 1H), 6.77 (d, J=7.96, 1H), 5.20 (s, 2H), 2.31 (s, 3H). ^{19}F NMR ($CDCl_3$ 282 MHz)

-62.11(s). High resolution mass spectrum calc'd. for $C_{18}H_{15}F_3N_3O_3S$ (MH^+): 410.0786. Found: 410.0754.

EXAMPLE 29



4-[6,8-Difluoro-1,5-dihydro-7-methoxy-3-(trifluoromethyl)[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 2,6-difluoroanisole.

A solution of 2,6-difluorophenol (30.00 g, 230 mmol) in 2.5 N sodium hydroxide (95 mL, 238 mmol) was treated with dimethylsulfate (33.32 g, 264 mmol) and stirred for 3.3 hours at 50 °C. Additional dimethylsulfate (13.33 g, 105 mmol) was added and the reaction was stirred another 0.6 hour. The reaction mixture was extracted with ethyl acetate, washed with 2.5 N sodium hydroxide, brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a clear oil (25.93 g, 78%): ^1H NMR ($CDCl_3$ 300 MHz) 6.87 (m, 3H) 3.98 (s, 3H); ^{19}F NMR ($CDCl_3$ 282 MHz) -129.48 (t). Mass spectrum: M+=144.

Step 2. Preparation of 2,4-difluoro-3-methoxybenzoic acid.

A solution of potassium tert-butoxide (22.74 g, 203 mmol) in anhydrous tetrahydrofuran (235 mL) was cooled to -78 °C and treated with a 1.6 M solution of n-butyllithium (120 mL, 192 mmol) in hexanes. After stirring for 30 minutes, 2,6-difluoroanisole (Step 1) (25.89 g, 180 mmol) was added and the reaction was stirred an additional 7.4

hours. The reaction was poured into dry ice and warmed to room temperature. Water (250 mL) was added, and after extracting with ether (160 mL), the aqueous layer was acidified with concentrated HCl, and filtered to give a yellow solid (3.71 g, 11%): mp 176-182 °C. ^{1}H NMR ($CDCl_3$ 300 MHz) 7.70 (m, 1H) 6.98 (m, 1H) 4.01 (s, 3H); ^{19}F NMR ($CDCl_3$ 282 MHz) -119.06 (m) -123.33 (m). Mass spectrum: M+Li=195.

<u>Step 3. Preparation of 2,4-difluoro-3-methoxybenzyl alcohol.</u>

A solution of 2,4-difluoro-3-methoxybenzoic acid (Step 2) (3.65 g, 19 mmol) in anhydrous tetrahydrofuran (24 mL) was cooled in an ice bath, and treated with borane dimethyl sulfide complex (4 mL, 40 mmol). The reaction was stirred at room temperature for 17 hours, quenched by the slow addition of methanol, and concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a brown oil (2.93 g, 87%): ^{1}H NMR ($CDCl_3$ 300 MHz) 7.01 (m, 1H) 6.86 (m, 1H) 4.66 (s, 2H) 3.97 (s, 3H); ^{19}F NMR ($CDCl_3$ 282 MHz) -129.67(m) -135.09 (m). Mass spectrum: M+=174.

<u>Step 4. Preparation of 2,4-difluoro-3-methoxybenzyl chloride.</u>

A solution of 2,4-difluoro-3-methoxybenzyl alcohol (Step 3) (2.93 g, 17 mmol) in concentrated HCl (15 mL) was treated with HCl gas for 3 minutes. The reaction was stirred at room temperature (21 hours). The reaction mixture was extracted with ether, dried over $MgSO_4$, and concentrated *in vacuo* to give a brown oil (2.30 g, 71%): ^{1}H NMR ($CDCl_3$ 300 MHz) 7.03 (m, 1H) 6.89 (m, 1H) 4.58 (s, 2H) 4.01 (s, 3H); ^{19}F NMR ($CDCl_3$ 282 MHz) -127.88 (m) -132.78 (m). Mass spectrum: M+=192.

<u>Step 5. Preparation of S-(2,4-difluoro-3-methoxybenzyl)-isothiouronium chloride.</u>

Thiourea (0.90 g, 12 mmol) was added to a solution of 2,4-difluoro-3-methoxybenzyl chloride (Step 4) (2.30 g, 12 mmol) in methanol (7 mL). The reaction was heated to reflux for 2.9 hours and concentrated *in vacuo* to give a white solid (3.18 g, 100%): mp 144-151 °C. ^{1}H NMR (DMSO-d_6 300 MHz) 9.35 (br. d, 3H) 7.26 (m, 1H) 7.15 (m, 1H) 4.57 (s, 2H) 3.91 (s, 3H); ^{19}F NMR (DMSO-d_6 282 MHz) -128.73 (m) -131.41 (m).

Step 6. Preparation of 3-(2,4-difluoro-3-methoxyphenylthio)propanoic acid.

A 100 mL flask was charged with the thiouronium salt from Step 5 (3.18 g, 12 mmol), sodium chloroacetate (2.36 g, 20 mmol), ethanol (10 mL), and water (10 mL). After heating to reflux, a solution of NaOH (2.51 g, 63 mmol) in water (10 mL) was added to the reaction dropwise. After stirring for 15.5 hours, the reaction was acidified with concentrated HCl, extracted with ether, washed with brine, dried over $MgSO_4$, concentrated *in vacuo*, and recrystallized from ether/hexane to give a brown oil (2.33 g, 70%): ^{1}H NMR ($CDCl_3$ 300 MHz) 8.4 (br. s, 1H) 6.98 (m, 1H) 6.85 (m, 1H) 3.99 (s, 3H) 3.85 (s, 2H) 3.17 (s, 2H); ^{19}F NMR ($CDCl_3$ 282 MHz) -129.33 (m) -132.16 (m). Mass spectrum: M+Li=255.

Step 7. Preparation of 6,8-difluoro-7-methoxyisothiochroman-4-one.

The acid from Step 6 (2.30 g, 9.3 mmol) was dissolved in trifluoroacetic acid (10 mL), treated with trifluoroacetic anhydride (5 mL) and stirred at room temperature for 1.3 hours. The reaction was poured into 10% Na_2CO_3 (150 mL) and extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a brown solid (0.45 g) which was used in the next step without further purification.

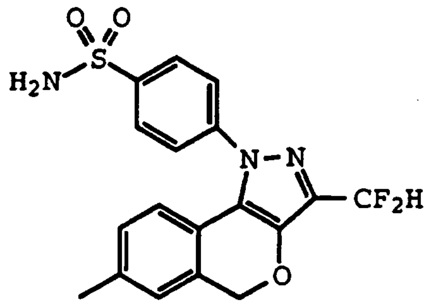
Step 8. Preparation of 6,8-difluoro-7-methoxy- 3-(trifluoroacetyl)isothiochroman-4-one.

Ethyl trifluoroacetate (0.30 g, 2.1 mmol) was added to a solution of the isothiochromanone from Step 7 (0.45 g, 2.0 mmol) in ether (5 mL). The reaction was treated with 25 weight % NaOMe (0.52 g, 2.4 mmol) and stirred at room temperature for 6.5 hours, then treated with 3N HCl. The organic layer was collected, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a brown oil (0.43 g) which was used in the next step without further purification.

Step 9. Preparation of 4-[6,8-difluoro-1,5-dihydro-7-methoxy-3-(trifluoromethyl)[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

The 4-sulfonamidophenylhydrazine hydrochloride (0.38 g, 1.7 mmol) was added to a stirred solution of the diketone (Step 8) (0.43 g, 1.3 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred for 16.6 hours. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*, dissolved in ethyl acetate, washed with water and brine, dried over $MgSO_4$, concentrated *in vacuo*, and passed through a column of silica gel to give the pyrazole as a brown oil (0.23 g, 37%): ^1H NMR (acetone-d_6 300 MHz) 8.11 (d, J=8.7 Hz, 2H) 7.87 (d, J=8.7 Hz, 2H) 6.84 (br s, 2H) 6.57 (d, J=11.9 Hz, 1H) 4.20 (s, 2H) 4.03 (t, J=1.0 Hz, 3H); ^{19}F NMR (acetone-d_6 282 MHz) -63.33 (s) -130.85 (m) -132.61 (m). High resolution mass spectrum calc'd. for $C_{18}H_{12}F_5N_3O_3S_2$: 477.0240. Found: 477.0205.

EXAMPLE 30



4-[3-(Difluoromethyl)-1,5-dihydro-7-methyl[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of (3-methylphenyl)-3-oxo-propanoic acid.

A solution of 3-methylbenzyl alcohol (4.93 g, 40 mmol), chloroacetic acid (7.68 g, 81 mmol), and ethanol (0.04 mL) in 100 mL of anhydrous tetrahydrofuran was added to a mixture of sodium hydride (16.12 g, 403 mmol) in 50 mL anhydrous tetrahydrofuran dropwise over 55 minutes at 0 °C. The cooling bath was removed and the solution was heated to reflux for 14.25 hours. The solution was cooled to room temperature, quenched with water and extracted with ether. The aqueous layer was acidified, extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give (3-methylphenyl)-3-oxo-propanoic acid as an orange oil (6.58 g) which also contained chloroacetic acid. The oil was used in the next step without purification.

Step 2. Preparation of 7-methylisochroman-4-one.

The acid from Step 1 (6.58 g, 36 mmol) was dissolved in trifluoroacetic acid (20 mL), treated with trifluoroacetic anhydride (11 mL) and stirred at room temperature for 14.75 hours. The reaction was poured into 10% Na_2CO_3 (150 mL) and extracted with ether, washed with brine, dried over $MgSO_4$, concentrated *in vacuo*, and passed

through a column of silica gel with 15% ethyl acetate/hexane to give a yellow solid (1.09 g, 18%): ^{1}H NMR ($CDCl_3$ 300 MHz) 7.95 (d, J=7.9 Hz, 1H) 7.23 (d, J=7.9 Hz, 1H) 7.02 (s, 1H) 4.85 (s, 2H) 4.34 (s, 2H) 2.42 (s, 3H).

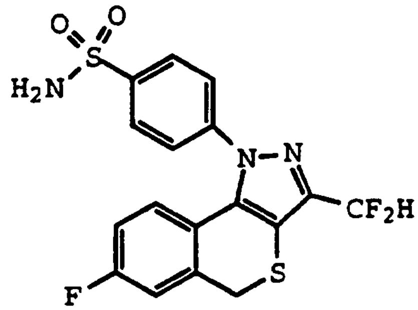
Step 3. Preparation of 3-(difluoroacetyl)-7-methylisochroman-4-one.

Ethyl difluoroacetate (1.02 g, 8.2 mmol) was added to a solution of the isochromanone from Step 2 (1.07 g, 6.6 mmol) in ether (20 mL). The reaction was treated with 25 weight % NaOMe (1.89 g, 8.7 mmol) and stirred at room temperature for 3.1 hours. The reaction mixture was filtered to give a yellow solid which was dissolved in 3N HCl, extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow solid (0.79 g) which was used in the next step without further purification.

Step 4. Preparation of 4-[3-(difluoromethyl)-1,5-dihydro-7-methyl[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

4-Sulfonamidophenylhydrazine hydrochloride (0.77 g, 3.4 mmol) was added to a stirred solution of the diketone from Step 3 (0.75 g, 3.1 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred for 2.25 hours. The reaction mixture was filtered while hot and recrystallized from ethyl acetate/hexane to give a yellow solid (0.41 g, 34%): mp 178-179 °C (dec). ^{1}H NMR (DMSO-d_6 300 MHz) 8.00 (d, J=8.7 Hz, 2H) 7.84 (d, J=8.5 Hz, 2H) 7.56 (br s, 2H) 7.25 (s, 1H) 7.12 (t, J=53.6 Hz, 1H) 7.08 (d, J=8.1 Hz, 1H) 6.72 (d, 8.1 Hz) 5.28 (s, 2H) 2.29 (s, 3H); ^{19}F NMR (DMSO-d_6 282 MHz) -114.42 (d). High resolution mass spectrum calc'd. for $C_{18}H_{15}F_2N_3O_3S$: 391.0802. Found: 391.0798.

EXAMPLE 31



4-[3-(Difluoromethyl)-1,5-dihydro-7-fluoro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

<u>Step 1. Preparation of S-(3-fluorobenzyl)-isothiouronium chloride.</u>

A solution of 3-fluorobenzyl chloride (49.95 g, 0.346 mol) dissolved in 60 mL of anhydrous methanol was treated portion wise with thiourea (26.30 g, 0.346 mol) over a period of 0.25 hour at room temperature. The solution was warmed to reflux for 0.5 hour, cooled to 5 °C and the product was isolated by filtration to afford 59.17 g. Concentration of the filtrate and chilling in an ice bath afforded an additional 9.93 g of pure S-(3-fluorobenzyl)isothiouronium chloride (96%): mp 201-203 °C.

<u>Step 2. Preparation of 3-(3-fluorophenylthio)propanoic acid.</u> S-(3-Fluorobenzyl)-isothiouronium chloride from step 1 (25.0 g, 94 mmol) was added to sodium chloroacetate (16.4 g, 141 mmol), sodium hydroxide pellets (15.0 g, 376 mmol), ethanol (150 mL), and water (100 mL). This mixture was stirred for 16 hours at room temperature, then concentrated hydrochloric acid was added to pH 1. The solution was extracted with ether (2 X 100 mL), combined and washed with brine, dried over $MgSO_4$, and concentrated. A brown solid was recrystallized from ether/hexanes (18.7 g, 95%): mp 86-88 °C.

Step 3. Preparation of 7-fluoroisothiochroman-4-one.

3-(3-Fluorophenylthio)propanoic acid from step 2 (18.0 g, 90 mmol) was dissolved in trifluoroacetic acid (30 mL), treated with trifluoroacetic anhydride (90 mL) and heated to reflux for 16 hours. Ether (200 mL) was added, and the mixture was washed with saturated aqueous $NaHCO_3$ solution (2 X 150 mL) and water. After drying over $MgSO_4$, the solution was concentrated to a brown solid (13.0 g, 79%). This material was used in the next step without further purification or characterization.

Step 4. Preparation of 3-difluoroacetyl-7-fluoro-isothiochroman-4-one.

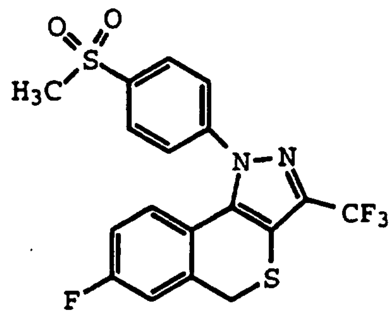
7-Fluoroisothiochroman-4-one from step 3 (2.0 g, 11 mmol) was dissolved in anhydrous ethyl ether (50 mL). Sodium methoxide 25% in methanol (2.61 g, 12 mmol) and ethyl difluoroacetate (1.49 g, 12 mmol) were added. After stirring for 16 hours at room temperature the mixture was washed with 1 N hydrochloric acid, brine, and water, dried over $MgSO_4$ and concentrated. This crude material was used in the next step without further purification or characterization.

Step 5. Preparation of 4-[3-(difluoromethyl)-1,5-dihydro-7-fluoro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

7-Fluoro-3-(difluoroacetyl)isothiochroman-4-one from Step 4 (2.9 g, 11 mmol) was dissolved in ethanol (100 mL), and 4-sulfonamidophenylhydrazine hydrochloride (2.68 g, 12 mmol) was added. The mixture was heated to reflux for 16 hours. After cooling, water was added until crystals appeared. A dark brown solid was collected by filtration (1.7 g, 37%): mp 260-262 °C. ^1H NMR (DMSO-d_6 300 MHz) 7.96 (d, J=8.4 Hz, 2H), 7.75 (d, J=8.4 Hz, 2H), 7.54 (s, 2H), 7.42 (dd, J=2.7, 9.3 Hz, 1H), 7.17 (t, J=53.7 Hz, 1H), 7.09 (dt, J=2.4, 8.4 Hz, 1H), 6.77 (dd, J=5.4, 8.7 Hz, 1H), 4.15

(s, 2H). Anal. calc'd. for $C_{17}H_{12}N_3S_2O_2F_3$: C, 49.63; H, 2.94; N, 10.21. Found: C, 49.55; H, 2.95; N, 10.14.

EXAMPLE 32



1,5-Dihydro-7-fluoro-1-[(4-methylsulfonyl)phenyl]-3-(trifluoromethyl)-[2]benzothiopyrano[4,3,c]pyrazole

Step 1. Preparation of 7-fluoro-3-trifluoroacetyl)isothiochroman-4-one.

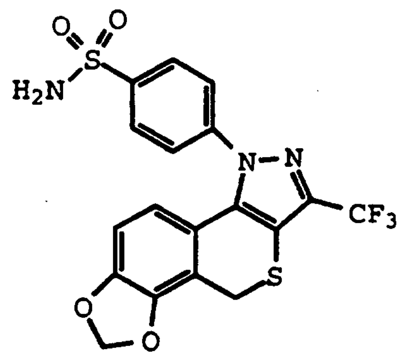
7-Fluoroisothiochroman-4-one (Example 31, step 3) (1.82 g, 10 mmol) was dissolved in anhydrous ethyl ether (50 mL). Sodium methoxide 25% in methanol (2.38 g, 11 mmol) and ethyl trifluoroacetate (1.56 g, 11 mmol) were added. After stirring for 16 hours at room temperature the mixture was washed with 1 N hydrochloric acid, brine, and water, dried over $MgSO_4$ and concentrated. This crude material was used in the next step without further purification or characterization.

Step 2. Preparation of 1,5-dihydro-7-fluoro-1-[(4-methylsulfonyl)phenyl]-3-(trifluoromethyl)-[2]benzothiopyrano[4,3,c]pyrazole.

7-Fluoro-3-trifluoroacetyl)isothiochroman-4-one (2.9 g, 11 mmol) from Step 1 was dissolved in ethanol (100 mL) and p-methanesulfonylphenylhydrazine hydrochloride (2.45 g, 11 mmol) was added. The mixture was heated to reflux for 16 hours, and concentrated. The resultant solid was dissolved in ethyl acetate and washed with brine and water,

dried over $MgSO_4$ and concentrated. A dark brown solid was recrystallized from ethyl acetate/hexanes (1.4 g, 32%): mp 193-195 °C. ^1H NMR (DMSO-d_6 300 MHz) 8.10 (d, J=8.7 Hz, 2H), 7.86 (d, J=8.7 Hz, 2H), 7.44 (dd, J=2.7, 9.3 Hz, 1H), 7.09 (dt, J=2.7, 8.7 Hz, 1H), 6.79 (dd, J=5.7, 8.7 Hz, 1H), 4.2 (s, 2H), 3.27(s, 3H). Anal. calc'd. for $C_{18}H_{12}N_2S_2O_2F_4$: C, 50.46; H, 2.82; N, 6.54. Found: C, 50.54; H, 2.84; N, 6.57.

EXAMPLE 33



4-[1,5-Dihydro-6,7-methylenedioxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 2,3-methylenedioxybenzoic acid.

1,3-Benzodioxole (12.2 g, 100 mmol) was dissolved in tetrahydrofuran (150 mL). This mixture was cooled to -78 °C under nitrogen with stirring while n-butyllithium 1.6 M in hexane (69 mL, 110 mmol) was added dropwise maintaining the temperature below -50 °C. Potassium t-butoxide (12.34 g, 110 mmol) was added and the mixture stirred at -78 °C for 0.25 hour when dry solid carbon dioxide was added. The cooling bath was removed and the mixture was stirred for an additional hour, when it was poured into 250 mL of 1 N hydrochloric acid. The mixture was extracted (3 X 100 mL) with ethyl acetate, combined and the organic portions were extracted into 2.5 N sodium hydroxide solution (2 X 50 mL).

The combined basic aqueous layers were acidified to pH 3 with 1 N hydrochloric acid and extracted with ethyl acetate (3 X 50 mL). The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated. A light brown solid was recrystallized from ethyl acetate/hexanes (2.9 g, 17%): mp 224-227 °C. ^1H NMR (DMSO-d_6 300 MHz) 12.9 (bs, 1H), 7.26 (dd, J=1.2, 8.1 Hz, 1H), 7.10 (dd, J=0.9, 7.5 Hz, 1H), 6.87 (dd, J=8.1, 7.8 Hz, 1H), 6.10 (s, 2H). Anal. calc'd for $C_8H_6O_4$: C, 57.84; H, 3.64. Found: C, 57.70; H, 3.73.

Step 2. Preparation of 2,3-methylenedioxybenzyl alcohol.

2,3-Methylenedioxybenzoic acid from Step 1 (2.8 g, 17 mmol) was dissolved in tetrahydrofuran (100 mL) and borane-dimethyl sulfide complex (10 M) was added (5.0 mL, 50 mmol). This mixture was stirred for 16 hours when methanol was added dropwise to destroy unreacted borane. Ethyl acetate (100 mL) was added and the mixture was washed with saturated aqueous $NaHCO_3$ solution and water twice, dried over $MgSO_4$, and concentrated to 2.4 g of a light brown solid. This material was used in the next step without further purification or characterization.

Step 3. Preparation of S-(2,3-methylenedioxybenzyl)-isothiouronium chloride.

A solution of 2,3-methylenedioxybenzyl alcohol from Step 2 (2.4 g, 16 mmol) was dissolved in tetrahydrofuran (25 mL). Triethylamine (2.43 g, 24 mmol) was added followed by the dropwise addition of methanesulfonyl chloride (2.27 g, 20 mmol). After stirring at room temperature for 4 hours, thiourea (1.3 g, 16 mmol) and methanol (50 mL) were added. The mixture was heated to reflux for 16 hours, concentrated and used in the next step without further purification or characterization.

Step 4. Preparation of 3-(2,3-methylenedioxyphenylthio)propanoic acid.

S-(2,3-Methylenedioxybenzyl)-isothiouronium chloride from Step 3 (3.4 g, 16 mmol), sodium chloroacetate (2.8 g, 24 mmol), sodium hydroxide pellets (2.6 g, 64 mmol), ethanol (25 mL), and water (40 mL) were combined and stirred for 16 hours at room temperature. Concentrated hydrochloric acid was added to pH 1, and the solution was extracted with ether (4 X 50 mL). The combined ethereal layers were washed with 1 N hydrochloric acid, dried over $MgSO_4$, and concentrated (3.62 g, 95%). This mixture was used in the next step without further purification or characterization.

Step 5. Preparation of 6,7-methylenedioxyisothiochroman-4-one. 3-(2,3-Methylenedioxyphenylthio)propanoic acid from Step 4 (3.62 g, 16 mmol) was dissolved in trifluoroacetic acid (5 mL), treated with trifluoroacetic anhydride (15 mL) and stirred at room temperature for 16 hours. After neutralizing with saturated aqueous $NaHCO_3$, the solution was extracted with ethyl acetate (3 X 50 mL). The combined organic extracts were washed with brine and concentrated. Purification was performed by flash column chromatography eluting with (4:1) hexanes:ethyl acetate. The appropriate fractions were concentrated and recrystallized from ethyl acetate/hexanes to yield a brown solid (0.5 g, 15%): mp 114-116 °C. ^1H NMR (DMSO-d_6 300 MHz) 7.56 (d, J=8.4 Hz, 1H), 6.95 (d, J=8.1 Hz, 1H), 6.16 (s, 2H), 3.87(s, 2H), 3.57(s, 2H). Anal. calc'd. for $C_{10}H_8O_3S$: C, 57.68; H, 3.87. Found: C, 57.59; H, 3.93

Step 6. Preparation of 6,7-methylenedioxy-3-(trifluoroacetyl) isothiochroman-4-one.

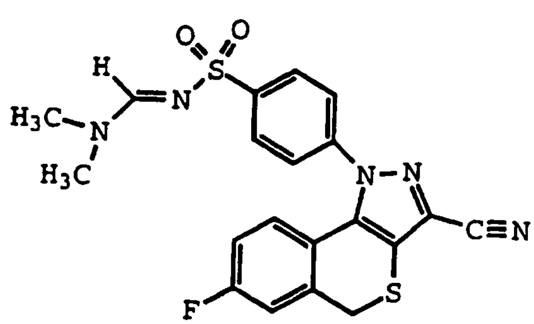
6,7-Methylenedioxyisothiochroman-4-one from Step 5 (0.44 g, 2.1 mmol) was dissolved in anhydrous ethyl ether (50 mL). Sodium methoxide 25% in methanol (0.54 g, 2.5 mmol) and ethyl trifluoroacetate (0.36 g, 2.5 mmol) were added. After stirring for 16 hours at room temperature the mixture was washed with 1 N hydrochloric acid, brine, and

water, dried over $MgSO_4$ and concentrated. This crude material was used in the next step without further purification or characterization.

Step 7. Preparation of 4-[1,5-dihydro-7-fluoro-3-(difluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

6,7-Methylenedioxy-3-(trifluoroacetyl)isothiochroman-4-one from Step 6 (0.64 g, 2.1 mmol) was dissolved in ethanol (100 mL) and 4-sulfonamidophenylhydrazine hydrochloride (0.56 g, 2.5 mmol) was added. The mixture was heated to reflux for 16 hours, and concentrated. The resultant oily solid was dissolved in ethyl acetate and washed with brine and water, dried over $MgSO_4$ and concentrated. Purification was achieved by flash column chromatography eluting with (1:1) ethyl acetate:hexanes. The appropriate fractions were concentrated and recrystallized from ethyl acetate/hexanes. The product was a light brown solid (0.2 g, 21%): mp 272-274 °C. ^1H NMR (DMSO-d_6 300 MHz) 7.98 (d, J=8.4 Hz, 2H), 7.78 (d, J=8.7 Hz, 2H), 7.44 (bs, 2H), 6.79 (d, J=8.4 Hz, 1H), 6.28 (d, J=8.1 Hz, 1H), 6.14 (s, 2H), 4.09 (s, 2H). Anal.s calc'd for $C_{18}H_{12}N_3S_2O_4F_3$: C, 47.47; H, 2.66; N, 9.23. Found: C, 47.56; H, 2.73; N, 9.16.

EXAMPLE 34



4-(3-Cyano-1,5-dihydro-7-fluoro-[2]benzothiopyrano[4,3-

c]pyrazol-1-yl)-N-[(dim thylamino)methylene]-benzenesulfonamide

Step 1. Preparation of 3,4-dihydro-α,4-dioxo-7-fluoro-1H-2-benzothiopyran-3-acetic acid, methyl ester.

7-Fluoroisothiochroman-4-one (Example 31, step 3) (2.0 g, 11 mmol) was dissolved in anhydrous ethyl ether (50 mL), and sodium methoxide 25% in methanol (2.6 g, 12 mmol), and dimethyl oxalate (1.42 g, 12 mmol) were added. After stirring for 16 hours at room temperature, the mixture was washed with 1 N hydrochloric acid, brine, and water, dried over $MgSO_4$, concentrated. A brown solid was recrystallized from chloroform/hexanes (2.5 g, 85%): mp 133-135 °C. ^1H NMR (DMSO-d_6 300 MHz) 15.4 (s, 1H), 8.03 (dd, J=5.7, 8.7 Hz, 1H), 7.11 (dt, J=2.4, 8.4 Hz, 1H), 6.94(dd, J=2.7, 8.7 Hz, 1H), 3.95(s, 3H), 3.78 (s, 2H). Anal. calc'd. for $C_{12}H_9N_3SO_4F$: C, 53.73; H, 3.38. Found: C, 53.56; H, 3.42.

Step 2. Preparation of 4-[3-(carbomethoxy)-1,5-dihydro-7-fluoro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

3,4-Dihydro-α,4-dioxo-7-fluoro-1H-2-benzothiopyran-3-acetic acid, methyl ester from Step 1 (2.5 g, 9 mmol) was dissolved in methanol (100 mL) and p-sulfonamidophenylhydrazine hydrochloride (2.23 g, 10 mmol) was added. The mixture was heated to reflux for 16 hours. After cooling, water was added until crystals appeared. The product was collected by filtration and recrystallized from methanol/water to yield a dark brown solid (3.6 g, 95%): mp 241-244 °C. ^1H NMR (DMSO-d_6 300 MHz) 7.99 (d, J=8.4 Hz, 2H), 7.8 (d, J=8.4 Hz, 2H), 7.56 (s, 2H), 7.42 (dd, J=2.4, 9.0 Hz, 1H), 7.08 (dt, J=2.7, 8.7 Hz, 1H), 6.75 (dd, J=5.4, 8.7 Hz, 1H), 4.18 (s, 2H), 3.85 (s, 3H). Anal. calc'd. for $C_{18}H_{14}N_3O_4S_2F_1$: C, 51.54; H, 3.36; N, 10.02. Found: C, 51.38; H, 3.44; N, 9.94.

Step 3. Preparation of 4-[3-(carboxamido)-1,5-dihydro-7-fluoro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide.

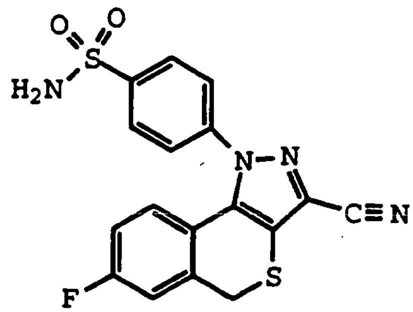
4-[3-(Carbomethoxy)-1,5-dihydro-7-fluoro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide from Step 2 (1.0 g, 2.4 mmol), methanol (50 mL), and sodium cyanide (0.5 g) were placed in a Parr bottle and pressurized to 20 psig with ammonia gas. After stirring for 64 hours at room temperature, the mixture was concentrated, dissolved in ethyl acetate, and washed with 1 N hydrochloric acid, and water. The solution was then dried over $MgSO_4$ and concentrated. A white solid was recrystallized from ethyl acetate/hexanes (0.6 g, 62%): mp 297-298 °C. ^1H NMR (DMSO-d_6 300 MHz) 7.97 (d, J=8.7 Hz, 2H), 7.78 (d, J=8.7 Hz, 2H), 7.74 (bs, 1H), 7.53 (s, 2H), 7.51 (bs, 1H), 7.39 (dd, J=2.7, 9.3 Hz, 1H), 7.07 (dt, J=2.7, 9.0 Hz, 1H), 6.75 (dd, J=5.4, 8.7 Hz, 1H), 4.1 (s, 2H). Anal. calc'd. for $C_{17}H_{13}N_4O_3S_2F$: C, 50.49; H, 3.24; N, 13.85. Found: C, 50.67; H, 3.35; N, 13.60.

Step 4. Preparation of 4-(3-cyano-1,5-dihydro-7-fluoro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl)-N-[(dimethylamino)methylene]-benzenesulfonamide.

N,N'-Dimethylformamide (3 mL) was cooled with stirring to 0 °C and oxalyl chloride (0.7 g, 5.5 mmol) was added dropwise. 4-[3-(Carboxamido)-1,5-dihydro-7-fluoro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide from Step 3 (1.0 g, 2.5 mmol) was dissolved in 2 mL of N,N'-dimethylformamide, added dropwise. The mixture was warmed to room temperature over 0.5 hour when pyridine (2 mL) was added followed by ethyl acetate (100 mL). After washing with 1 N hydrochloric acid, brine and water, the mixture was dried over $MgSO_4$ and concentrated. A light brown solid was recrystallized from ethyl acetate/hexanes (0.8 g, 73%): mp 232-235 °C. ^1H NMR (DMSO-d_6 300 MHz) 8.26 (s, 1H), 7.95 (d, J=8.7 Hz, 2H), 7.76 (d, J=8.7 Hz, 2H), 7.45 (dd, J=2.7, 9.3 Hz, 1H), 7.13 (dt, J=2.4, 8.4 Hz, 1H),

6.75 (dd, J=5.4, 8.7 Hz, 1H), 4.22 (s, 2H), 3.16 (s, 3H), 2.94(s, 3H). Anal. calc'd. for $C_{20}H_{16}N_5O_2S_2F + 0.5\ H_2O$: C, 53.32; H, 3.80; N, 15.54. Found: C, 53.33; H, 3.78; N, 15.50.

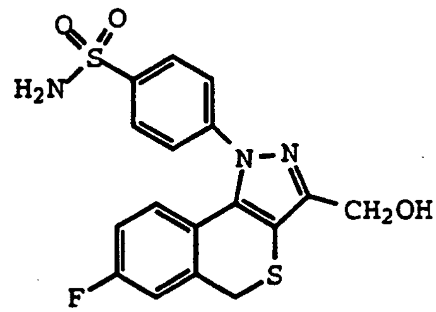
EXAMPLE 35



4-[3-Cyano-1,5-dihydro-7-fluoro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

4-(1,5-Dihydro-7-fluoro-3-cyano-[2]benzothiopyrano[4,3-c]pyrazol-1-yl)-N-[(dimethylamino)methylene]benzenesulfonamide (Example 34) (0.7 g, 1.6 mmol) was dissolved in tetrahydrofuran (50 mL) and treated with sodium hydroxide 2.5 N (10 mL). After stirring for 5 minutes, concentrated hydrochloric acid was added to pH 1. The mixture was extracted with ethyl acetate (2 X 30 mL), combined, washed with water, dried over $MgSO_4$, and concentrated. A tan solid was recrystallized from ethanol/water (0.6 g, 97%): mp 256-257 °C. ^1H NMR (DMSO-d_6 300 MHz) 8.00 (d, J=8.7 Hz, 2H), 7.81 (d, J=8.7 Hz, 2H), 7.58 (s, 2H), 7.46 (dd, J=2.7, 9.3 Hz, 1H), 7.11 (dt, J=2.4, 8.4 Hz, 1H), 6.77 (dd, J=5.4, 8.7 Hz, 1H), 4.22 (s, 2H). Anal. calc'd. for $C_{17}H_{11}N_4O_2S_2F$: C, 52.84; H, 2.87; N, 14.50. Found: C, 52.69; H, 2.95; N, 14.60.

EXAMPLE 36



4-[1,5-Dihydro-7-fluoro-3-(hydroxymethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide

4-[3-(Carbomethoxy)-1,5-dihydro-7-fluoro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide (Example 34, Step 2)(1.0 g, 2.4 mmol) was dissolved in tetrahydrofuran (50 mL) with stirring at room temperature. Lithium aluminum hydride 1.0 M in tetrahydrofuran (5 mL) was added dropwise. After 0.5 hour, 1.25 N sodium hydroxide (10 mL) was added. The mixture was filtered, concentrated, and purified by flash column chromatography eluting with ethyl acetate : hexanes (2:1). The appropriate fractions were concentrated and recrystallized from ethyl acetate/hexanes. Product was a white solid (0.2 g, 21%): mp 186-190 °C. ^{1}H NMR (DMSO-d_6 300 MHz) 7.92 (d, J=8.7 Hz, 2H), 7.66 (d, J=8.7 Hz, 2H), 7.49 (s, 2H), 7.46 (dd, J=2.7, 9.6 Hz, 1H), 7.11 (dt, J=2.7, 8.7 Hz, 1H), 6.77 (dd, J=5.7, 8.7 Hz, 1H), 5.72 (t, J=5.7 Hz, 1H), 4.49 (d, J= 5.7 Hz, 2H), 4.04 (s, 2H). Anal. calc'd. for $C_{17}H_{14}N_3S_2O_3F$: C, 52.16; H, 3.61; N, 10.73. Found: C, 52.42; H, 3.69; N, 10.49.

The following compounds were obtained according to procedures similar to that exemplified above and in the Gen ral Synthetic Schemes.

37) 4-[7-chloro-1,5-dihydro-3-trifluoromethyl-thieno[3',2':4,5]thiopyrano-s-oxide[3,2-c]pyrazol-1-yl]benzenesulfonamide: mp = 185°C (dec).

38) 4-[3-(difluoromethyl)-1,5-dihydro-6-fluoro-7-methoxy-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide: mp = 256-258°C.

39) 4-[1,5-dihydro-7-fluoro-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide: mp = 240-242°C.

40) [1-(4-aminosulfonylphenyl)-1,5-dihydro-7-fluoro-[2]benzothiopyrano[4,3-c]pyrazol-3-yl]carboxamide: mp = 297-298°C.

41) 4-[1,5-dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano-S-oxide[4,3-c]pyrazol-1-yl]benzenesulfonamide: mp = >300°C.

42) methyl [1-(4-aminosulfonylphenyl)-1,5-dihydro-7-fluoro-[2]benzothiopyrano[4,3-c]pyrazol-3-yl]carboxylate: mp = 241-244°C.

43) 4-[4,6-dihydro-7-fluoro-8-methoxy-3-(trifluoromethyl)-[2]benzothiepino[5,4-c]pyrazol-1-yl]benzenesulfonamide: mp = 133-138°C.

BIOLOGICAL EVALUATION

Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test was performed with materials, reagents and procedures essentially as described by Winter, et al., (*Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962)). Male Sprague-Dawley rats were selected in each group so that the average body weight was as close as possible. Rats were

fasted with free access to water for over sixteen hours prior to the test. The rats were dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One hour later a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline was administered and the volume of the injected foot was measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot was again measured. The average foot swelling in a group of drug-treated animals was compared with that of a group of placebo-treated animals and the percentage inhibition of edema was determined (Otterness and Bliven, *Laboratory Models for Testing NSAIDs*, in **Non-steroidal Anti-Inflammatory Drugs**, (J. Lombardino, ed. 1985)). The % inhibition shows the % decrease from control paw volume determined in this procedure and the data for selected compounds in this invention are summarized in Table XVII.

Rat Carrageenan-induced Analgesia Test

The analgesia test using rat carrageenan was performed with materials, reagents and procedures essentially as described by Hargreaves, et al., (*Pain*, **32**, 77 (1988)). Male Sprague-Dawley rats were treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats were placed in a special plexiglass container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty minute period, thermal stimulation was begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell turned off the

lamp and timer when light was interrupted by paw withdrawal. The time until the rat withdraws its foot was then measured. The withdrawal latency in seconds was determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal determined. Results are shown in Table XVII.

TABLE XVII.

	RAT PAW EDEMA % Inhibition[1]	ANALGESIA % Inhibition[1]
Example		
1	43	35
2	28	29
21	26	14

1- @ 30 mg/kg body weight

Evaluation of COX-1 and COX-2 activity *in vitro*

The compounds of this invention exhibited inhibition *in vitro* of COX-2. The COX-2 inhibition activity of the compounds of this invention illustrated in the Examples was determined by the following methods.

a. Preparation of recombinant COX baculoviruses

A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 was cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses were isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells (2x10e8) along with 200 ng of

linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses were purified by three rounds of plaque purification and high titer (10E7 - 10E8 pfu/ml) stocks of virus were prepared. For large scale production, SF9 insect cells were infected in 10 liter fermentors (0.5×10^6/ml) with the recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate was centrifuged at 10,000xG for 30 minutes, and the resultant supernatant was stored at -80°C before being assayed for COX activity.

b. Assay for COX-1 and COX-2 activity:

COX activity was assayed as PGE_2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme were incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 µM). Compounds were pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after ten minutes at 37 °C/room temperature by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE_2 formed was measured by standard ELISA technology (Cayman Chemical). Results are shown in Table XVIII.

TABLE XVIII.

Example	Human COX-2 IC50 µM	Human COX-1 IC50 µM
1	<0.1	2.7
2	<0.1	>100
3	1.3	7.1
4	0.5	
5	4.8	24.4
6	23.5	11.1
7	0.5	9.7
8	0.5	
9	48.2	>100
10	<0.1	6.2
11	52	>100
12	95	>100
13	<0.1	<0.1
14	0.2	4.6
15	<0.1	0.3
16	<0.1	0.4
17	<0.1	0.8
18	<0.1	3.7
19	<0.1	0.3
20	<0.1	<0.1
21	<0.1	8.7
22	3.5	51
24	<0.1	1.2
25	<0.1	1.5
26	<0.1	0.2
27	59.9	>100
28	<0.1	>100
29	0.3	>100
30	<0.1	10.7
31	<0.1	0.2
32	0.2	8.9
33	<0.1	<0.1
34	4.2	>100

TABLE XVIII. (cont.)

Example	Human COX-2 IC_{50} μM	Human COX-1 IC_{50} μM
35	0.1	0.8
36	1.7	6.7
37	45.6	91.1
38	<0.1	>100
39	<0.1	0.3
40	4.7	>100
41	1.2	>100
42	0.8	13.2
43	2.2	73.4

Biological paradigms for testing the cytokine-inhibiting activity of these compounds are found in WO95/13067, published 18 May 1995.

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of this combination therapy in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and composition may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of

a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.5 and about 20 mg/kg body weight and most preferably between about 0.1 to 10 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

For inflammations of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an

oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers

suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The antiinflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

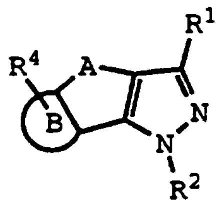
For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate,

magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What is claimed is:

1. A compound of Formula I



(I)

wherein A is $-(CH_2)_m-X-(CH_2)_n-$;

wherein X is selected from $S(O)_p$, O and NR^3;

wherein m is 0 to 3, inclusive;

wherein n is 0 to 3, inclusive;

wherein p is 0 to 2, inclusive;

wherein B is selected from aryl and heteroaryl;

wherein R^1 is selected from hydrido, halo, haloalkyl, cyano, nitro, formyl, alkoxycarbonyl, carboxyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, aminocarbonyl, alkoxy, alkoxyalkyl, aminocarbonylalkyl, N-alkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, N-alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N,N-dialkylaminosulfonyl, N-alkyl-N-arylaminosulfonyl and heterocyclic;

wherein R^2 is selected from aryl and heteroaryl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals selected from alkylsulfonyl, aminosulfonyl, halo, alkyl, alkoxy, hydroxyl and haloalkyl;

wherein R^3 is selected from hydrido and alkyl; and

wherein R^4 is one or more radicals selected from hydrido, halo, alkylthio, alkylsulfinyl, alkyl,

alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, amido, N-alkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, aminosulfonyl, N-alkylaminosulfonyl, amino, N-alkylamino, N,N-dialkylamino, heterocyclic, nitro and acylamino;

provided either R^4 is aminosulfonyl or alkylsulfonyl, or R^2 is substituted with aminosulfonyl or alkylsulfonyl;

or a pharmaceutically-acceptable salt thereof.

2. Compound of Claim 1 wherein A is $-(CH_2)_m-X-(CH_2)_n-$; wherein X is selected from $S(O)_p$, O and NR^3; wherein m is 0 to 3, inclusive; wherein n is 0 to 3, inclusive; wherein p is 0 to 2, inclusive; wherein B is selected from phenyl, naphthyl and five and six membered heteroaryl; wherein R^1 is selected from halo, lower haloalkyl, cyano, nitro, formyl, lower alkoxycarbonyl, lower carboxyalkyl, lower alkoxycarbonylalkyl, amidino, cyanoamidino, lower alkoxy, lower alkoxyalkyl, aminocarbonyl, lower aminocarbonylalkyl, lower N-alkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl, lower alkylcarbonyl, lower alkylcarbonylalkyl, lower hydroxyalkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkylthioalkyl, lower alkylsulfinylalkyl, lower alkylsulfonylalkyl, lower N-alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, lower N,N-dialkylaminosulfonyl, lower N-alkyl-N-phenylaminosulfonyl and five-seven membered heterocyclic; wherein R^2 is selected from phenyl and five or six membered heteroaryl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals selected from lower alkylsulfonyl, aminosulfonyl, halo, lower alkyl, lower

alkoxy, hydroxyl and lower haloalkyl; wherein R^3 is selected from hydrido and lower alkyl; and wherein R^4 is one or more radicals selected from hydrido, halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkylsulfonyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower N-alkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, aminosulfonyl, lower N-alkylaminosulfonyl, amino, lower N-alkylamino, lower N,N-dialkylamino, five-seven membered heterocyclic, nitro and acylamino; or a pharmaceutically-acceptable salt thereof.

3. Compound of Claim 2 wherein A is $-(CH_2)_m-X-(CH_2)_n-$; wherein X is $S(O)_p$ or O; wherein m is 0, 1 or 2; wherein n is 0, 1 or 2; wherein p is 0, 1 or 2; wherein B is selected from phenyl and five and six membered heteroaryl; wherein R^1 is selected from halo, lower haloalkyl, cyano, formyl, lower alkoxycarbonyl, aminocarbonyl, lower alkoxycarbonylalkyl, lower alkoxy, lower alkoxyalkyl, lower aminocarbonylalkyl, lower N-alkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl and lower hydroxyalkyl; wherein R^2 is phenyl substituted at a substitutable position with a radical selected from lower alkylsulfonyl and aminosulfonyl; and wherein R^4 is one or more radicals selected from hydrido, halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkylsulfonyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower N-alkylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, amino, lower N-alkylamino,

lower N,N-dialkylamino, lower haloalkoxy and nitro; or a pharmaceutically-acceptable salt thereof.

4. Compound of Claim 3 wherein A is $-(CH_2)_m$-X-$(CH_2)_n$-; wherein X is $S(O)_p$ or O; wherein m is 0 or 1; wherein n is 0 or 1; wherein p is 0 or 1; wherein B is selected from phenyl and five and six membered heteroaryl; wherein R^1 is selected from lower haloalkyl, lower hydroxyalkyl, cyano, formyl, lower alkoxycarbonyl, lower alkoxy, lower N-alkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl and lower N-alkyl-N-phenylaminocarbonyl; wherein R^2 is phenyl substituted at a substitutable position with a radical selected from lower alkylsulfonyl and aminosulfonyl; and wherein R^4 is one or more radicals selected from hydrido, halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, amino, lower N-alkylamino, lower N,N-dialkylamino, lower hydroxyalkyl and lower haloalkoxy; or a pharmaceutically-acceptable salt thereof.

5. Compoud of Claim 4 wherein A is $-(CH_2)_m$-X-$(CH_2)_n$-; wherein X is $S(O)_p$ or O; wherein m is 0 or 1; wherein n is 0 or 1; wherein p is 0 or 1; wherein B is selected from phenyl, thienyl, pyridyl, furyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, thiaimidazolyl, oxoimidazolyl, azaoxazolyl, azathiazolyl and pyrrolyl; wherein R^1 is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxymethyl,

hydroxyethyl, cyano, formyl, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, aminocarbonyl, methoxy, ethoxy, propoxy, n-butoxy, N-methylaminocarbonyl, N-phenylaminocarbonyl, N,N-dimethylaminocarbonyl, N-methyl-N-phenylaminocarbonyl and methylcarbonyl; wherein R^2 is phenyl substituted at a substitutable position with a radical selected from methylsulfonyl and aminosulfonyl; wherein R^4 is optionally substituted with one or more radicals selected from hydrido, fluoro, chloro, bromo, methylthio, ethylthio, isopropylthio, *tert*-butylthio, isobutylthio, hexylthio, methylsulfinyl, ethylsulfinyl, isopropylsulfinyl, *tert*-butylsulfinyl, isobutylsulfinyl, hexylsulfinyl, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, hexyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, aminocarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, hydroxymethyl and trifluoromethoxy; or a pharmaceutically-acceptable salt thereof.

6. Compound of Claim 5 selected from compounds, and their pharmaceutically acceptable salts, of the group consisting of.

6-fluoro-7-methoxy-1-[(4-methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-[1]benzothieno[3,2-c]pyrazole;

4-[6-fluoro-7-methoxy-3-(trifluoromethyl)-1H-[1]benzothieno[3,2-c]pyrazol-1-yl]benzenesulfonamide;

4-[6-methoxy-3-(trifluoromethyl)-1H-[1]benzothieno[3,2-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-fluoro-3-(trifluoromethyl)-1H-[1]benzothieno[3,2-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-chloro-3-(trifluoromethyl)-1H-[1]benzothieno[3,2-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-methyl-3-(trifluoromethyl)-1H-[1]benzothieno[3,2-c]pyrazol-1-yl]benzenesulfonamide;

4-[3-(trifluoromethyl)-1H-[1]benzothieno[3,2-c]pyrazol-1-yl]benzenesulfonamide;

6-fluoro-7-methoxy-1-[(4-methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-[1]benzofuro[3,2-c]pyrazole;

4-[6-fluoro-7-methoxy-3-(trifluoromethyl)-1H-[1]benzofuro[3,2-c]pyrazol-1-yl]benzenesulfonamide;

4-[6-methoxy-3-(trifluoromethyl)-1H-[1]benzofuro[3,2-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-fluoro-3-(trifluoromethyl)-1H-[1]benzofuro[3,2-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-chloro-3-(trifluoromethyl)-1H-[1]benzofuro[3,2-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-methyl-3-(trifluoromethyl)-1H-[1]benzofuro[3,2-c]pyrazol-1-yl]benzenesulfonamide;

4-[3-(trifluoromethyl)-1H-benzofuro[3,2-c]pyrazol-1-yl]benzenesulfonamide;

1,5-dihydro-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazole;

1,5-dihydro-7-methyl-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazole;

1,5-dihydro-6-fluoro-7-methoxy-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazole;

4-[1,5-dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-7-fluoro-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[6-chloro-1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-chloro-1,5-dihydro-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[6,7-difluoro-1,5-dihydro-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-1,5-dihydro-6-fluoro-7-methoxy-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

1,4-dihydro-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazole;

1,4-dihydro-7-methyl-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazole;

1,4-dihydro-6-fluoro-7-methoxy-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazole;

4-[1,4-dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-7-fluoro-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[6-chloro-1,4-dihydro-7-methoxy-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-chloro-1,4-dihydro-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-7-methoxy-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-7-methyl-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[6,7-difluoro-1,4-dihydro-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-1,4-dihydro-6-fluoro-7-methoxy-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-1,5-dihydro-7-methyl-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-7,8,9-trimethoxy-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-7-methyl-3-(trifluoromethyl)-[2]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

methyl [1-[4-(aminosulfonyl)phenyl]-1,4-dihydro-[1]benzopyrano[4,3-c]pyrazol-3-yl]carboxylate;

methyl [1-(4-aminosulfonylphenyl)-1,5-dihydro-7-fluoro-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-3-yl]carboxylate;

methyl [1-(4-aminosulfonylphenyl)-1,5-dihydro-7-fluoro-[2]benzothiopyrano[4,3-c]pyrazol-3-yl]carboxylate;

4-[7-chloro-3-(difluoromethyl)-1,5-dihydro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-3-(trifluoromethyl)-[1,3]dioxolo[6,7][2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-fluoro-1,5-dihydro-3-(hydroxymethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-1,5-dihydro-7-methyl-[2]benzenethiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[3-cyano-7-fluoro-1,5-dihydro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]-N-[(dimethylamino)methylene]benzenesulfonamide;

4-[3-(difluoromethyl)-7-fluoro-1,5-dihydro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[3-cyano-7-fluoro-1,5-dihydro-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[6,8-difluoro-1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

7-fluoro-1,5-dihydro-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazole;

[1-(4-aminosulfonylphenyl)-1,5-dihydro-7-fluoro-[2]benzothiopyrano[4,3-c]pyrazol-3-yl]carboxamide;

[1-(4-aminosulfonylphenyl)-1,5-dihydro-7-fluoro-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-3-yl]carboxamide;

4-[3-(difluoromethyl)-1,5-dihydro-6-fluoro-7-methoxy-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-7-fluoro-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

1,5-dihydro-6-fluoro-7-methoxy-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazole;

4-[1,5-dihydro-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-7-methyl-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

1-[1,5-dihydro-4-(methylsulfonyl)phenyl]-7-methyl-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazole;

4-[7-chloro-1,5-dihydro-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-chloro-1,5-dihydro-3-trifluoromethyl-thieno[3',2':4,5]thiopyrano[3,2-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-chloro-1,5-dihydro-3-trifluoromethyl-thieno[3',2':4,5]thiopyrano-S-oxide[3,2-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-3-(trifluoromethyl)furano[2',3':4,5]thiopyrano[3,2-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-3-(trifluoromethyl)oxazolo[4',5':4,5]thiopyrano[3,2-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,5-dihydro-3-(trifluoromethyl)thiazolo[5',4':4,5]thiopyrano[3,2-c]pyrazol-1-yl]benzenesulfonamide;

1,5-dihydro-1-(4-methoxyphenyl)-3-(trifluoromethyl)thieno[3',2':4,5]thiopyrano[3,2-c]pyrazole-7-sulfonamide;

4-[1,5-dihydro-3-(trifluoromethyl)pyrazolo[3',4':5,6]thiopyrano[3,4-b]pyridin-1-yl]benzenesulfonamide;

4-[1,5-dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano-S-oxide[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

methyl [1-[4-(aminosulfonyl)phenyl]-1,4-dihydro-[1]benzothiopyrano[4,3-c]pyrazol-3-carboxylate;

4-[6,7-dichloro-1,4-dihydro-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-7-fluoro-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-6-isopropyl-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-7,8-dimethoxy-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-7-methoxy-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-7-methyl-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[6-chloro-1,4-dihydro-7-methoxy-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[1,4-dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[7-chloro-1,4-dihydro-3-(trifluoromethyl)-[1]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide;

4-[4,6-dihydro-7-fluoro-8-methoxy-3-(trifluoromethyl)-[1]benzothiepino[5,4-c]pyrazol-1-yl]benzenesulfonamide; and

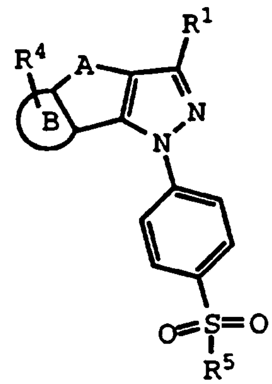
1-(4-aminosulfonylphneyl)-1,4-dihydro[1]benzothiopyrano[4,3-c]pyrazole-3-yl]carbonitrile.

7. Compound of Claim 5 which is 4-[1,5-dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

8. Compound of Claim 5 which is 1-[6-fluoro-7-methoxy-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1,5-dihydro-[2]benzothiopyrano[4,3-c]pyrazole, or a pharmaceutically-acceptable salt thereof.

9. Compound of Claim 5 which is 4-[7-chloro-1,5-dihydro-3-trifluoromethyl-[2]thienothiopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

10. A compound of Formula II



(II)

wherein A is $-(CH_2)_m-X-(CH_2)_n-$;
wherein X is $S(O)_p$ or O;
wherein m is 0 or 1;
wherein n is 0 or 1;
wherein p is 0 or 1;
wherein B is selected from aryl and heteroaryl;
wherein R^1 is selected from haloalkyl, hydroxyalkyl, aminocarbonyl, alkoxycarbonyl and cyano;
wherein R^4 is one or more radicals selected from hydrido, halo, alkyl and alkoxy; and
wherein R^5 is selected from alkyl and amino;
or a pharmaceutically-acceptable salt thereof.

11. Compound of Claim 10 wherein A is $-(CH_2)_m-X-(CH_2)_n-$; wherein X is $S(O)_p$ or O; wherein m is 0 or 1; wherein n is 0 or 1; wherein p is 0 or 1; wherein B is selected from phenyl and five membered heteroaryl; wherein R^1 is selected from lower haloalkyl, lower hydroxyalkyl, aminocarbonyl, lower alkoxycarbonyl and cyano; wherein R^4 is one or more radicals selected from hydrido, halo, lower alkyl and lower alkoxy; and wherein R^5 is selected from lower alkyl and amino; or a pharmaceutically-acceptable salt thereof.

12. Compound of Claim 11 wherein A is $-(CH_2)_m-X-(CH_2)_n-$; wherein X is $S(O)_p$ or O; wherein m is 0 or 1;

wherein n is 0 or 1; wherein p is 0 or 1; wherein B is selected from phenyl, thienyl, furyl and pyrrolyl; wherein R^1 is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxymethyl, hydroxyethyl, aminocarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and cyano; wherein R^4 is one or more radicals selected from hydrido, fluoro, chloro, bromo, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, hexyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy and *tert*-butoxy; and wherein R^5 is selected from methyl and amino; or a pharmaceutically-acceptable salt thereof.

13. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 1, 2, 3, 4, 5, 6, 7, 8 or 9; or a pharmaceutically-acceptable salt thereof.

14. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said inflammation or inflammation-associated disorder, a therapeutically-effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, 7, 8 or 9; or a pharmaceutically-acceptable salt thereof.

15. The method of Claim 14 for use in treatment of inflammation.

16. The method of Claim 14 for use in treatment of an inflammation-associated disorder.

17. The method of Claim 16 wherein the inflammation-associated disorder is arthritis.

18. The method of Claim 16 wherein the inflammation-associated disorder is pain.

19. The method of Claim 16 wherein the inflammation-associated disorder is fever.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/11403

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D491/048 A61K31/415 C07D491/052 C07D495/04 C07D495/14 C07D513/14 //(C07D491/048,307:00,231:00),(C07D495/04,333:00,231:00),(C07D491/052,311:00,231:00),(C07D495/04,335:00,231:00),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 347 773 (FARMITALIA) 27 December 1989 cited in the application see claims 1,6	1,10,13
A	EP,A,0 203 679 (E. I. DU PONT) 3 December 1986 see page 193 - page 195; claim 1	1,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 December 1995	9.01.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Voyiazoglou, D

INTERNATIONAL SEARCH REPORT

Interna' l Application No
PCT/US 95/11403

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 (C07D495/04,337:00,231:00),(C07D495/14,335:00,231:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
27 December 1995	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Voyiazoglou, D

INTERNATI NAL SEARCH REPORT	Int. tional application No. PCT/US95/11403

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 14-19 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Intern. ... l Application No
PCT/US 95/11403

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		AU-B- 3769289	12-01-90
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		WO-A- 8912630	28-12-89
		EP-A- 0422051	17-04-91
		ES-T- 2054930	16-08-94
		IE-B- 63189	22-03-95
		IL-A- 90552	26-08-94
		JP-T- 3505205	14-11-91
		PT-B- 90905	30-12-94
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		CA-A- 1230334	15-12-87
		US-A- 4741765	03-05-88